cancer rates and risks

2nd Edition

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2ND EDITION, 1974

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ERRATA

9 - Table 3: male, age 65+, 16,756 deaths due to Asthma
should read "Bronchitis, Emphysema, and Asthma"

21 - Table 8: 98.6% of Prostate cancers are adenosarcomas
should read "adenocarcinomas"

25 - 5th line from bottom: ...majority of counties.
should read "countries"

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Foreword

The fight against cancer depends on the support of informed citizens. The first edition of Cancer Rates and Risks[1], published in 1964, has served as a useful reference volume for physicians, medical students, teachers, public health workers, and other individuals concerned with the course of the disease in individual patients or with its effect on various population groups. This revised edition takes note of new information collected since 1964 and contains an expanded section on patient survival.

Accumulation of facts about cancer in human populations dates back to Percival Pott's description of chimney sweeps' cancer around 1775 and the analysis by Rigoni Stern of the death certificates from Verona for the years 1760-1839. Epidemiologic observations assembled since that time have demonstrated that the frequency and distribution of specific forms of malignant neoplasms are related to a variety of factors, including sex, age, race, familial history of cancer, and exposure to potential carcinogens.

Several issues remain unresolved. For example, when differences in cancer risks are relatively small, their detection requires prolonged observation of large numbers of persons. Also, the long interval between exposure and the development of cancer may conceal some cause-effect relationships. Many group comparisons and their interpretation are complicated by differences in medical care facilities and in ability to recognize and diagnose the disease. Significant contributions to our knowledge have been made in recent years, but new findings pose new questions for investigation, and the need for more accurate, more complete, and more detailed information now seems greater than ever before.

Results obtained from special study approaches—such as retrospective studies of diagnosed cases and matched controls, forward studies of defined cohorts, and population screening tests—supplement the findings of mortality and morbidity reports. These study techniques have been used to investigate such diverse topics as the association of smoking and lung cancer, the relationship between carcinoma-in-situ and invasive cancer of the uterine cervix, the association of cancer of specific sites with other diseases, and the incidence of cancer among persons who have already had at least one malignant tumor. However, some of the individual findings are based on a relatively limited experience, and their interpretation requires cross-checking with other evidence and confirmation by other methods.

The questions and answers with accompanying charts and tables in this publication are based on the evidence now available.

The effects of cancer are felt in many ways such as personal loss, loss to society, financial loss, etc. Some of these variables are impossible to quantify and measure. There is need for study into many of the sociologic and psychologic aspects of cancer. Other variables can be measured and studied; the purpose of this report is to present information on some of the measurable aspects of cancer. The presentation covers variations and trends in cancer incidence and mortality, some aspects of diagnosis and treatment, the epidemiologic characteristics of the more important cancer sites, survival rates for diagnosed cancer cases, and prospects for future progress. The authors' statements on these issues are their considered opinions, often evolved in consultation with other staff members. Much interesting information has been omitted. The sources cited in the bibliography may be consulted for more detailed data and for further references. There are some questions that cannot be answered with present knowledge; we hope that some readers will be stimulated to help fill the gaps in our knowledge of cancer epidemiology.

In closing, I wish to refer to a theme which constantly recurs in the discussion of many topics treated in this book—"cancer is a group of diseases found in all races and ages of man. . . ." Within the United States the National Cancer Institute conducts research in cancer; sponsors and supports research by others; and within the framework of the National Cancer Plan, endeavors to coordinate research and related activities in a manner that will facilitate the timely application of new knowledge to the control of cancer in man, so that the toll of death and disability from this disease can be reduced. But cancer is more than a national problem and cancer research must be international in scope. Significant contributions have been made by scientists of many countries, often working in close cooperation at an international level. More extensive international cooperation among individual investigators as well as joint efforts under the auspices of governmental or international agencies, such as the International Agency for Research on Cancer of the World Health Organization and the International Union Against Cancer, can accelerate research progress and the dissemination and application of new knowledge.

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SECTION

1

cancer in the United States

SECTION 1

Cancer in the United States

1. What is cancer?

Cancer is a group of diseases found in all races and ages of man and in all other animal species. There are, however, marked differences in the occurrence of cancer by histologic type and by anatomic site, not only from species to species, but within human populations.

Physicians and laymen alike have often thought of cancer as a single disease. So it is, in the sense that all cancer is characterized by unrestrained growth of cells. In most cases these cells build up into tumors which compress, invade, and destroy normal tissues and which if untreated usually lead to death. Malignant tumors generally share some common characteristics, whatever the specific form of cancer involved. These include (1) a higher rate of cell growth than the normal tissues from which cancers are derived, (2) failure to maintain the boundaries of normal tissues and organs, (3) a microscopic appearance which suggests in some ways a resemblance to immature rather than mature tissues, and (4) a tendency to spread to parts of the body distant from the original site of the cancer. Not all of these features necessarily accompany every malignant tumor, but they are characteristic of most forms of cancer.

Despite these similarities, most observers are more impressed by the great differences among various forms of cancer. A careful description of any disease, including cancer, must cover many relevant factors such as the primary location of the pathologic process, the severity of the illness, related etiologic factors if known, and such data as the age and sex of the patient. This additional information is as necessary for statistical and epidemiologic studies as it is for assessment of the proper treatment and prognosis of individual patients. For many purposes it is better to think of "cancer" as a collection of diseases—skin cancer, lung cancer, leukemia, etc.

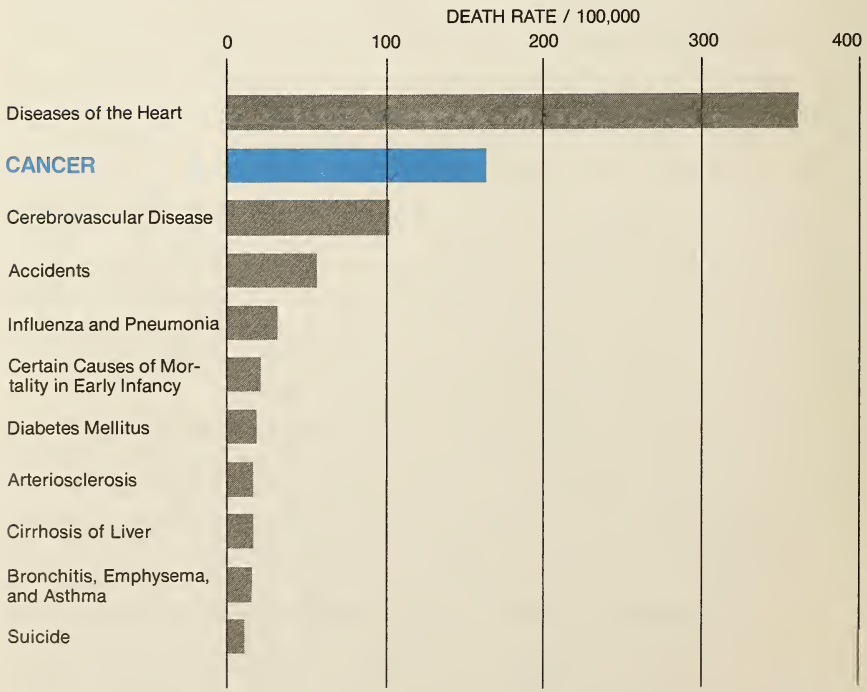
Even these more specific terms, based on the location where the tumor originated, include several distinct pathologic processes.

Not all tumors are cancer and not all cancers are inexorably fatal. In the United States there were an estimated 603,000 new cases of cancer diagnosed in 1970 and only 331,000 reported deaths due to cancer. Prompt and careful medical attention to any suspected cancer is required to reach a proper diagnosis and plan of treatment for each individual patient.

2. How does cancer compare with other diseases as a cause of death?

In 1900 tuberculosis was the leading cause of death in the United States, heart disease ranked fourth, and cancer ranked eighth. As treatment of infectious diseases improved, the number of deaths due to these diseases decreased. Today cancer is the second most frequent cause of death in the United States, accounting for 330,730 deaths in 1970 and 337,398 deaths in 1971. Figure 1 presents data

FIGURE 1. DEATH RATES FOR THE 11 LEADING CAUSES OF DEATH: United States, 1970



Source: [13]

TABLE 1. NUMBER OF ADMISSIONS PER PATIENT DURING TWO YEAR FOLLOW-UP PERIOD.

NUMBER OF HOSPITAL ADMISSIONS	NUMBER OF PATIENTS	PERCENT OF TOTAL
One	1935	61.4
Two	743	23.6
Three	267	8.5
Four	117	3.7
Five	45	1.4
Six or More	44	1.4
TOTAL	3151	100.0

Average number admissions per patient: 1.7 Source: unpublished data from [11]

for the 11 leading causes of death in 1970. Although there are some differences in mortality by race and sex, cancer ranks second for both males and females and in both the white and nonwhite populations of the United States.

References: [3, 13]

3. What are some of the economic costs of cancer?

Much of the financial burden of cancer is related to the need for hospital care. (See also Question 44.) Table 1 shows the number of admissions per patient during the two year period following diagnosis for a sample of 3151 cancer patients. Sixty-one percent of these patients required only one admission; the average number of admissions was 1.7 per patient. A typical in-patient hospital stay for a cancer patient lasts an average of 16 days and costs (in terms of actual payments made to hospitals from all sources) about $1400 per stay. Assuming there are 1.3 million cancer patients under hospital care each year in the United States, $1.8 billion per annum would be expended solely for this service. Doctor bills, outpatient therapy, time lost from work, and other disease-related costs would put the annual economic expenditure for cancer well into the tens of billions of dollars.

References: [11]

4. How can the extent of cancer illness be measured?

The essential requirement for arriving at objective measures of cancer illness is that the number of persons with cancer be related to

the population to which such persons belong. Three measures of disease are commonly employed:

1. Incidence rate: the number of new cases arising during a given time period in a specific population, usually measured by counting the number of newly diagnosed cancers in a given year. This is the measure most directly related to cancer risk and as such is of most interest to cancer epidemiologists. Preventive measures are aimed at stopping the onset of new cases and thus lowering cancer incidence. The accuracy of reported incidence rates is affected by errors in diagnosis and incompleteness of reporting. The National Cancer Institute is developing a program of population-based tumor registries to provide information on trends in the incidence of the various forms of cancer in the United States. These registries will cover approximately 10% of the total U.S. population. There is no system in the United States for nationwide reporting of cancer incidence.

2. Mortality rate: the number of deaths due to the disease occurring during a given time period in a specific population. In the United States, rates are computed from data gathered by the National Center for Health Statistics from death certificates. The major source of error in mortality rates is inaccurate determination of cause of death. Since mortality data are available for the entire country, they are frequently used as an indirect measure of cancer incidence. Mortality most closely reflects incidence for highly fatal diseases with a short survival period. As treatment improves, leading to fewer deaths due to cancer and to lengthened survival, mortality rates go down even without any change in incidence.

3. Prevalence rate: the number of cases existing at a given point in time in a specific population. In practice, it is difficult to measure a "point" prevalence. "Period prevalence" is usually measured as the number of people with cancer under medical care during some time period. Prevalence rates are used in administrative and health-care planning for estimating case loads and requirements of medical facilities. Another method of estimating prevalence is to combine data on annual incidence and survival rates. This method gives the number of people now alive who ever had cancer and includes both prevalent cases and persons cured of cancer. Table 2 shows the estimated number of persons in the population who are alive with a history of cancer, computed for the year 1971.

Although rates for specific populations are of intrinsic interest, their greatest value lies in the comparison of groups of people that differ with respect to age, sex, place of residence, or other factors. Various tables and figures in this report offer comparisons between these group-specific rates.

It is often necessary to compare incidence or mortality rates in

TABLE 2. PERSONS ALIVE IN 1971 WITH HISTORY OF CANCER: United States.

Breast	677,000
Colon/Rectum	495,000
Total Uterus	387,000
Prostate	201,000
Lung & Bronchus	85,000
Lymphomas	45,000
Stomach	39,000
Leukemias	37,000
Pancreas	5,000
Esophagus	4,000
All Sites*	2,922,000

*Excluding skin & carcinoma-in-situ. Source: computed from [4-7, 11]

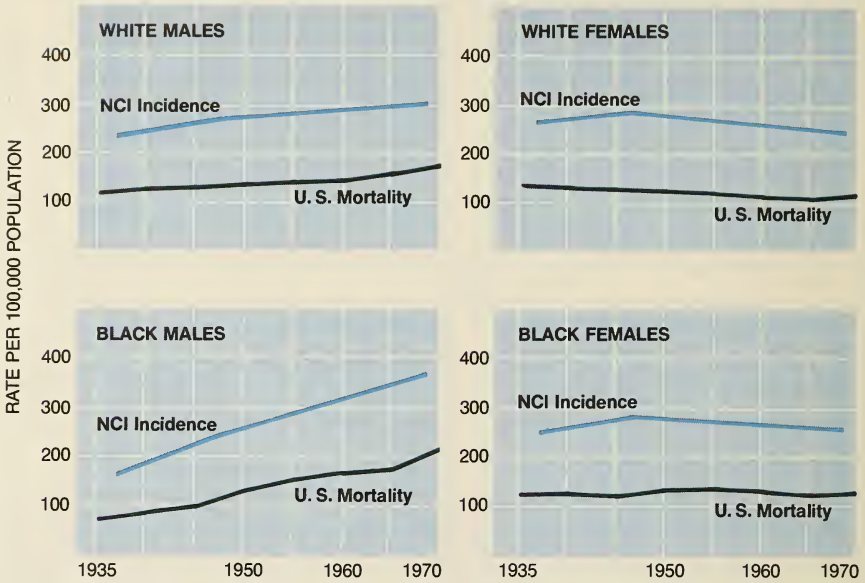
two or more populations which differ significantly with respect to factors which are of no immediate interest. Thus, for example, one may wish to compare the incidence of cancer in the United States with that in Ireland. Since the risk of cancer depends on age, a direct comparison would be complicated by the fact that the population of Ireland is, on the average, somewhat older than that of the United States. Such complications can be avoided by the use of adjusted rates, which mathematically remove the effects of age and other factors extraneous to the comparison. For example, in one method of adjusting rates for age, the age-specific rates for each population under study are applied to the same standard population and the resultant figures are then compared. Age and sex adjusted rates have been used frequently in preparation of this report. The exact methodology of these procedures is described more fully in many standard works.

References: [58, 68, 96]

5. How have incidence and mortality rates for cancer been changing?

In 1935 there were 137,649 cancer deaths recorded in the United States. In 1971 there were 337,398 recorded deaths. Part of the increase in deaths results from population growth and part is attributable to aging of the population. While some of the residual rise in reported cancer mortality may be accounted for by improved reporting of causes of death, most observers feel that there has been a true increase in the total cancer death rate. Figure 2 presents mortality data for the total United States and incidence data from

FIGURE 2. TIME TRENDS IN CANCER INCIDENCE AND MORTALITY BY RACE AND SEX: United States, 1935-1970 (age adjusted to 1950).



Source: [4, 11, 13]

three surveys conducted by the National Cancer Institute. Examination of race and sex specific rates shows a rise in mortality for both white and black males, steady trends for black females, and a decline for white females. Incidence rates for each sex-race group follow the same time trends portrayed by the mortality data.

The rising trend in men, in contrast to the falling trend in women, points to the need for increased research into both environmental (largely occupational) and sex-linked genetic etiologic factors.

References: [2, 3, 11, 13]

6. How does the occurrence of cancer vary with age and sex?

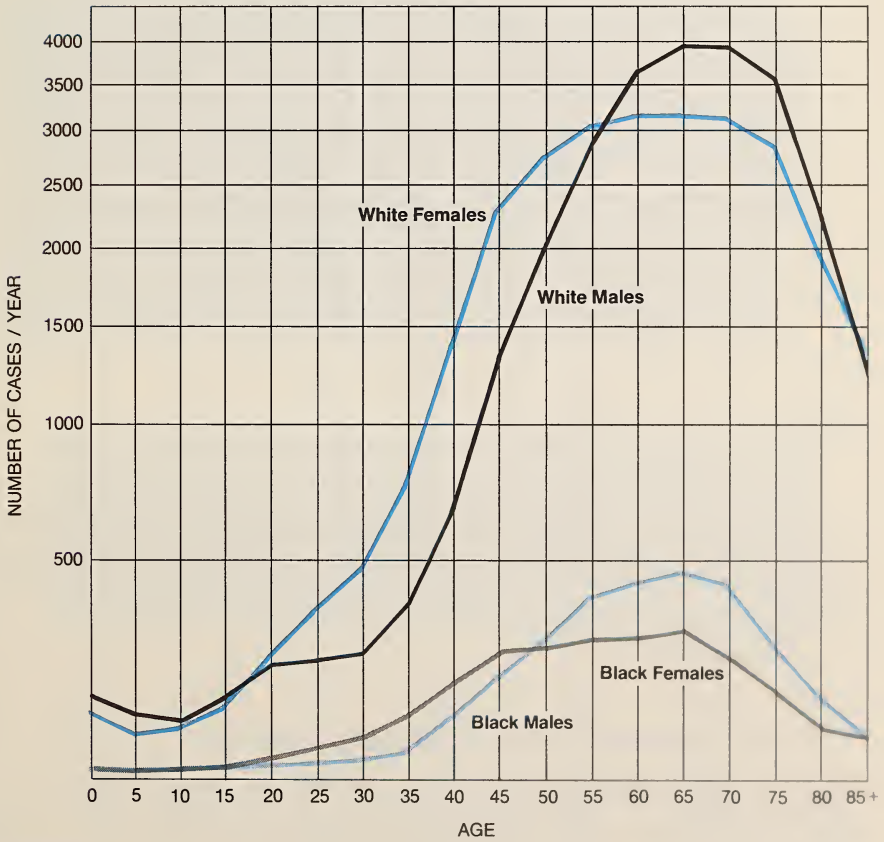
Cancer is predominantly a disease of middle and old age, rare in children and young adults. Figure 3 shows the annual number of cases by age for white and black males and females as reported during the Third National Cancer Survey.[*] The smaller number of

[*] The Third National Cancer Survey[11] encompasses an area with a population of over 20 million people, or about 10% of the population of the total United States. Information has been obtained by the TNCS on all cases of cancer seen in the survey area during the years 1969-1971.

black cases reflects population differences. Persons around age 70 account for a higher number of cases than any other age group. Cancer in women appears earlier; between the ages of 20 and 40 cancer is more than 3 times as common in women than in men. Between the ages of 50 and 80, men account for more cancer cases than women. Over all ages, women account for more cancer cases than men.

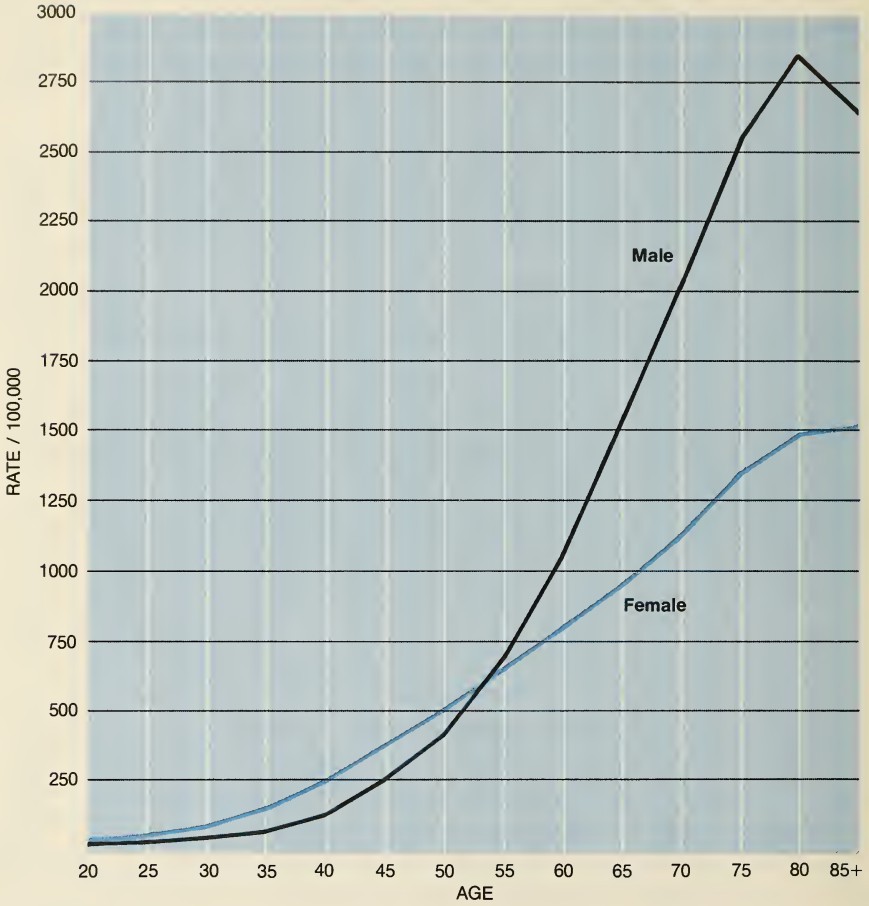
After age 70, the number of cases decreases, but so does the total population, causing incidence rates to continue to climb until the very oldest age group. Figure 4 shows age-specific incidence rates for males and females. In spite of the female preponderance of *number* of cases, age-specific population differences between the sexes cause the total cancer *rate* for men to be higher than that for women.

FIGURE 3. ANNUAL NUMBER OF CANCERS BY AGE, RACE, AND SEX: United States (10% sample), 1969-1971 (All sites except skin and carcinoma-in-situ).



Source: [11]

FIGURE 4. AGE-SPECIFIC CANCER INCIDENCE RATES BY SEX: United States, all races combined, all sites (except skin and carcinoma-in-situ), 1969-1971.



Source: [11]

Table 3 shows the five leading causes of death by age-group and sex for the year 1970. Cancer is the leading disease-related cause of death in women up to age 65 and in men between the ages of 5-25.

References: [2, 11, 13]

7. How common is cancer among children?

In 1970, 3620 children under the age of 15 years died of cancer in the United States. In this age group, there were 99,442 deaths from other causes. Thus for children under the age 15, cancer accounts

TABLE 3. MORTALITY, FIVE LEADING CAUSES OF DEATH, BY AGE GROUP AND SEX: United States, 1970, all races combined.

	ALL AGES		1-4		5-14		15-24		25-44		45-64		65+	
	MALE	FEMALE	MALE	FEMALE	MALE	FEMALE	MALE	FEMALE	MALE	FEMALE	MALE	FEMALE	MALE	FEMALE
1	Heart Diseases 417,918	Heart Diseases 317,624	Accidents 2,564	Accidents 1,736	Accidents 5,695	Accidents 2,508	Accidents 19,396	Accidents 4,940	Accidents 18,865	CANCER 9,902	Heart Diseases 128,955	CANCER 55,444	Heart Diseases 274,181	Heart Diseases 264,236
2	CANCER 180,157	CANCER 150,573	Congenital Malformations 694	Congenital Malformations 637	CANCER 1,389	CANCER 1,040	Homicide 3,333	CANCER 1,114	Heart Diseases 13,445	Accidents 5,114	CANCER 65,556	Heart Diseases 47,663	CANCER 102,769	Cerebrovascular Disease 96,738
3	Cerebrovascular Disease 93,456	Cerebrovascular Disease 113,710	Pneumonia, Influenza 601	CANCER 449	Congenital Malformations 481	Congenital Malformations 420	Suicide 2,378	Homicide 824	CANCER 7,939	Heart Diseases 4,793	Accidents 17,528	Cerebrovascular Disease 14,028	Cerebrovascular Disease 73,313	CANCER 82,511
4	Accidents 79,756	Accidents 34,882	CANCER 578	Pneumonia, Influenza 442	Pneumonia, Influenza 327	Pneumonia, Influenza 324	CANCER 1,817	Suicide 750	Suicide 5,866	Suicide 2,506	Cerebrovascular Disease 17,165	Accidents 6,636	Pneumonia, Influenza 21,434	Pneumonia, Influenza 18,778
5	Pneumonia, Influenza 35,148	Pneumonia, Influenza 27,591	Meningitis 141	Homicide 128	Homicide 215	Heart Diseases 162	Heart Diseases 642	Heart Diseases 412	Homicide 4,907	Cerebrovascular Disease 2,446	Cirrhosis 11,908	Cirrhosis 6,158	Asthma 16,756	Arteriosclerosis 17,336

Source: [13]

for 1 out of 28 deaths, compared to a figure for adults of 1 out of 6 deaths. In the first year of life the major causes of death are those associated with the birth process itself; in this age group cancer accounted for only 164 deaths during 1970.

Projections from available incidence data show that about 7000 new cases of cancer occur annually in children under the age of 15 years, a figure almost twice that of mortality. This large difference is due partially to long-term survivors who are diagnosed before the age of 15, but live long enough so that if they die of cancer, it is after the age of 15. Table 4 shows mortality figures for the most common

TABLE 4. CHILDHOOD CANCER MORTALITY, BY SITE AND AGE: United States, 1970, all races combined.

SITE	TOTAL (AGE <15)		NUMBER OF DEATHS BY AGE						
	PERCENT	NUMBER	<1	1	2	3	4	5-9	10-14
All sites	100.0	3,620	164	197	235	291	304	1,351	1,078
Respiratory system	0.8	30	5	1	3	2	2	8	9
Genital system	1.6	59	1	0	7	1	2	14	34
Digestive system	1.8	65	15	12	10	3	2	11	12
Urinary system	3.9	141	8	8	13	21	19	57	15
Connective tissue (includes bone, skin, breast)	7.9	286	10	11	12	11	5	76	161
Brain & Central Nervous system	24.3	880	45	70	70	78	72	319	226
Leukemia	46.2	1,672	68	82	98	137	169	684	434
Other Lymphatic and hematopoietic tumors	9.0	326	7	6	8	16	19	139	131
Other & unspecified sites	4.4	161	5	7	14	22	14	43	56
All causes of death	—	103,062	74,667	4,337	2,819	2,371	2,021	8,401	8,446

Source: [13]

forms of cancer in children. Table 5 presents incidence data according to tumor site and histology. Leukemia is the most common form of childhood cancer, followed by tumors of the central nervous system.

References: [11, 13, 130]

TABLE 5. CHILDHOOD CANCER INCIDENCE, BY SITE, HISTOLOGY, AND AGE: United States, 1969-1971, all races combined.

SITE	PERCENT OF CASES	AVERAGE ANNUAL INCIDENCE/100,000			
		CRUDE RATE (AGE <15)	AGE-SPECIFIC RATES		
			0-4	5-9	10-14
All Sites	100.0	14.18	20.43	11.64	11.52
Leukemia	32.4	4.60	7.77	3.64	2.95
Acute Lymphocytic		2.65	4.44	2.36	1.46
Acute Granulocytic		0.67	0.90	0.41	0.73
Other Acute		0.69	1.34	0.52	0.32
Chronic		0.14	0.24	0.07	0.12
Other & Unspecified		0.44	0.83	0.26	0.30
Brain & Central Nervous System	21.1	3.00	3.39	3.47	2.23
Astrocytoma		1.31	1.14	1.59	1.19
Medulloblastoma		0.51	0.50	0.71	0.32
Glioma		0.50	0.61	0.65	0.28
Neuroblastoma		0.15	0.52	0.00	0.01
Other		0.47	0.59	0.48	0.38
Lymphoma	10.4	1.48	0.83	1.55	1.93
Hodgkin's Disease		0.65	0.08	0.48	1.28
Lymphosarcoma		0.31	0.26	0.43	0.25
Reticulum Cell Sarcoma		0.09	0.00	0.18	0.08
Other		0.40	0.48	0.45	0.30
Kidney	6.7	0.95	2.13	0.69	0.23
Wilms' Tumor		0.87	2.00	0.65	0.17
Other		0.07	0.13	0.03	0.05
Bone	4.7	0.67	0.13	0.52	1.25
Osteogenic Sarcoma		0.37	0.02	0.22	0.80
Ewing's Sarcoma		0.17	0.02	0.22	0.25
Other		0.12	0.08	0.07	0.19
Connective Tissue	4.3	0.61	0.83	0.37	0.66
Rhabdomyosarcoma		0.20	0.26	0.18	0.17
Other		0.40	0.57	0.18	0.48
Eye & Orbit	3.2	0.46	1.43	0.13	0.00
Retinoblastoma		0.40	1.32	0.03	0.00
Other		0.06	0.11	0.09	0.00
Adrenal Gland	2.8	0.40	1.10	0.15	0.07
Other & Unspecified Sites	14.0	1.98	2.79	1.08	2.17

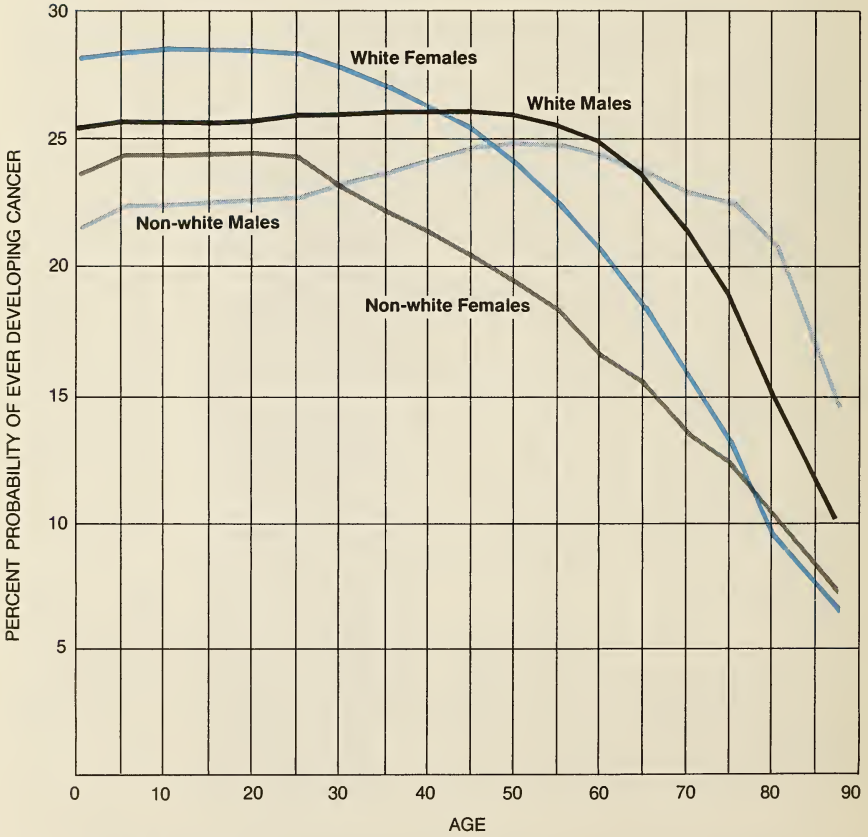
Source: [11]

8. What is the probability that a person will develop or die from cancer?

At present, the chance that a person now under the age of 20 years will develop cancer at some time during his or her life is about one in four for males and slightly higher for females, assuming that the general mortality rates and cancer incidence rates remain at their present levels.

The probability of developing cancer varies with age (figure 5). For instance, it is greater at age 20 than at birth because of appreciable infant mortality from non-malignant diseases. At older ages, however, the competition of other causes of death becomes an important factor lowering the risk of getting cancer. This is especially true for women whose chance of developing cancer in their remaining lifetimes is less after age 30 than it was at birth.

FIGURE 5. LIFETIME PROBABILITY OF DEVELOPING CANCER OF ANY SITE (excluding skin) BY AGE, SEX, AND RACE: United States, 1969.



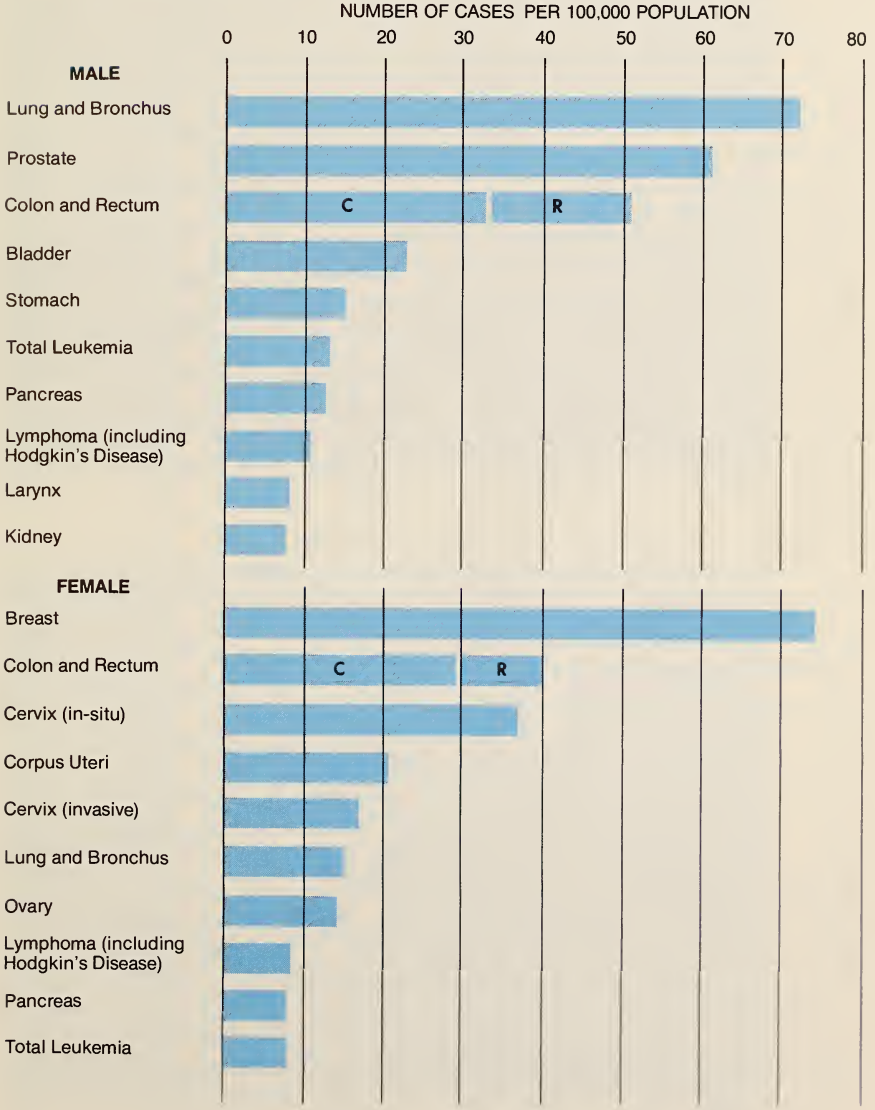
Source: computed from [11, 13]

Comparison between whites and nonwhites shows a greater risk for whites at all ages except for men over the age 65; in this age group nonwhites have high rates of cancer of the lung and prostate. If white women survive free of cancer past age 40, their risk be-

comes less than that of men of their same age. The corresponding age for nonwhites is age 30.

Since people with diagnosed cancer die of other causes, the probability of dying of cancer are somewhat below the correspond-

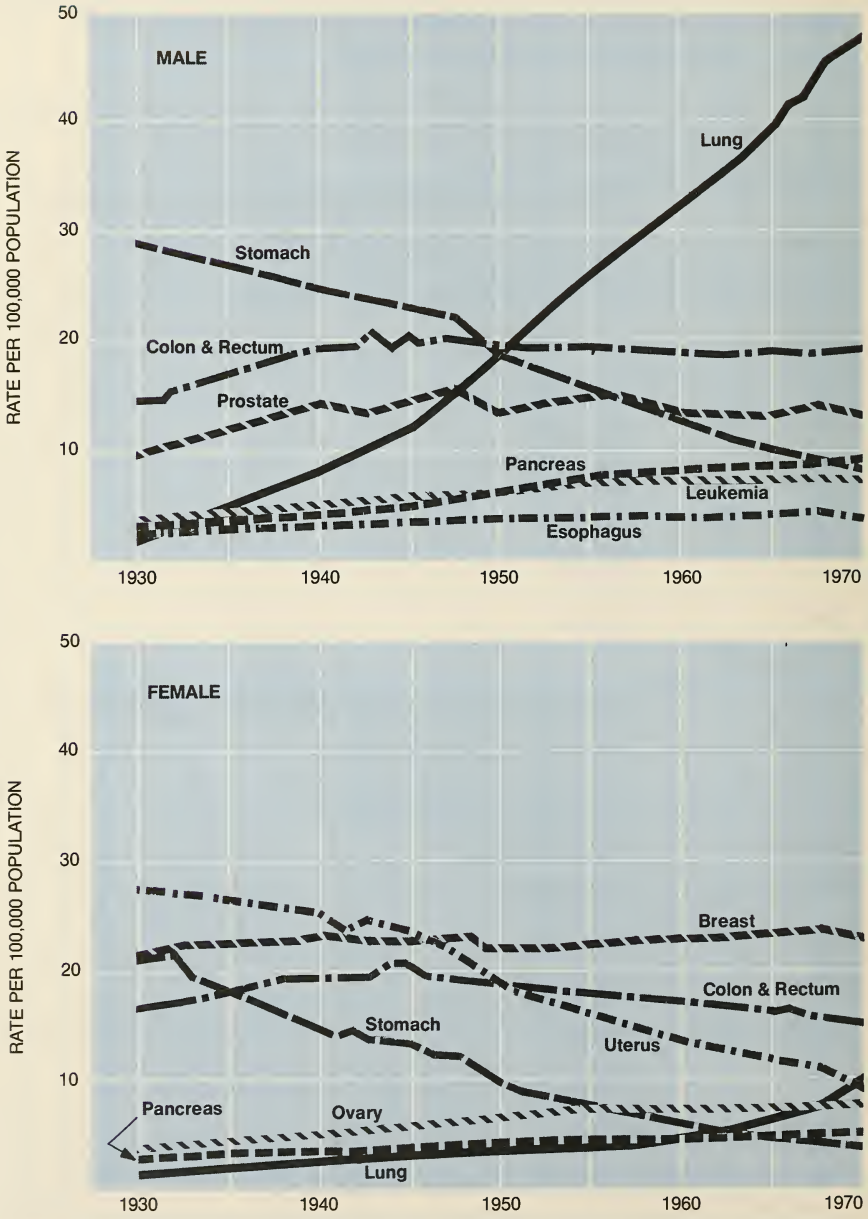
FIGURE 6. CANCER INCIDENCE BY SITE AND SEX: United States, 1969-1971 (age-adjusted to 1970 U. S. population).



Source: [11]

ing probabilities of developing cancer but in general show the same patterns with respect to age, sex, and race.

FIGURE 7. TIME TRENDS IN CANCER MORTALITY RATES, BY SITE AND SEX: United States, 1930-1970 (age-adjusted to U. S. 1940 population).



Source: [3.13]

9. How does the occurrence of cancer vary by site?

Figure 6 shows cancer incidence rates by site for each sex. For men lung cancer is the leading site, followed by cancers of the prostate, colon/rectum, bladder, and stomach. For women breast cancer is the most frequent site, followed by colon/rectum, uterus, lung, and ovary. Ranking site groups in order of mortality yields similar results: for women—breast, colon/rectum, lung, uterus, and ovary; for men —lung, colon/rectum, prostate, pancreas, and stomach.

References: [11, 13]

10. How has the frequency of cancer of specific sites been changing?

The changes over time for cancer incidence and mortality have not been uniform for all sites. Figure 7 shows time trends in mortality for the leading sites in men and women. Lung cancer in men has shown the most dramatic rise, increasing almost 20-fold in the last 40 years. Deaths from lung cancer in women are at a lower absolute level and have increased at a lower rate than for men, but are now increasing more quickly. Cancer of the stomach is decreasing in both sexes; the reason for this trend is not known but changes in diet are believed to be a contributing factor. Deaths due to uterine cancer have also decreased. Part of this change is related to improved diagnostic methods for detecting cancer of the cervix, but the death rates were already on their way down when cervical cytology programs were being implemented; therefore this decline cannot be totally explained by these programs.

Table 6 presents data from the TNCS and two earlier surveys conducted by the National Cancer Institute. The time trends seen in these incidence data parallel the trends observed in the mortality data.

References: [3, 11, 13]

11. Are there racial differences in the occurrence of cancer?

Until recently, age-adjusted cancer rates for whites have been higher than those for blacks, but the incidence and mortality rates for black males have been rising more rapidly than have rates for white males. (See figure 2.) The rates for black females have remained constant while rates for white females have fallen slightly. Consequently, today the rates for blacks (all sites combined) are higher than those for whites. These racial differences vary greatly from one site to another (figure 8). The cancer incidence rates for whites are higher than those for blacks in the following sites: colon/rectum, breast, bladder, uterine corpus, leukemia, lymphomas, and

TABLE 6. TIME TRENDS IN CANCER INCIDENCE RATES, BY SITE, RACE, AND SEX; three surveys conducted by NCI: 1937, 1947, and 1969.

SITE	RACE AND SEX	1937	1947	1969
Esophagus	White Male	7.8	8.3	6.0
	White Female	1.6	1.9	1.6
	Black Male	6.0	9.7	19.5
	Black Female	1.4	2.2	4.2
Stomach	White Male	44.0	34.1	14.0
	White Female	26.1	18.3	6.1
	Black Male	38.3	39.6	20.5
	Black Female	22.2	22.8	10.0
Colon	White Male	22.4	26.2	33.1
	White Female	24.0	27.8	27.6
	Black Male	13.2	13.9	26.4
	Black Female	11.8	16.2	37.1
Rectum	White Male	19.0	22.1	17.3
	White Female	12.2	15.2	10.7
	Black Male	8.0	12.7	13.1
	Black Female	8.4	13.6	9.9
Pancreas	White Male	7.0	9.3	11.3
	White Female	4.9	5.5	6.7
	Black Male	5.0	11.6	15.0
	Black Female	3.4	6.4	14.5
Lung	White Male	13.7	29.5	68.9
	White Female	4.0	6.5	13.5
	Black Male	8.4	25.4	84.7
	Black Female	3.4	5.8	18.2
Breast	White Female	66.2	72.6	75.2
	Black Female	49.4	53.9	67.8
Uterus (Total)	White Female	59.9	56.3	35.3
	Black Female	108.8	95.6	49.0
Ovary	White Female	12.7	14.7	13.3
	Black Female	5.5	9.9	11.4
Prostate	White Male	29.8	34.8	42.7
	Black Male	30.7	49.9	77.6
Bladder	White Male	15.3	18.6	22.5
	White Female	7.4	8.0	5.9
	Black Male	5.6	7.0	15.3
	Black Female	5.5	7.9	4.5

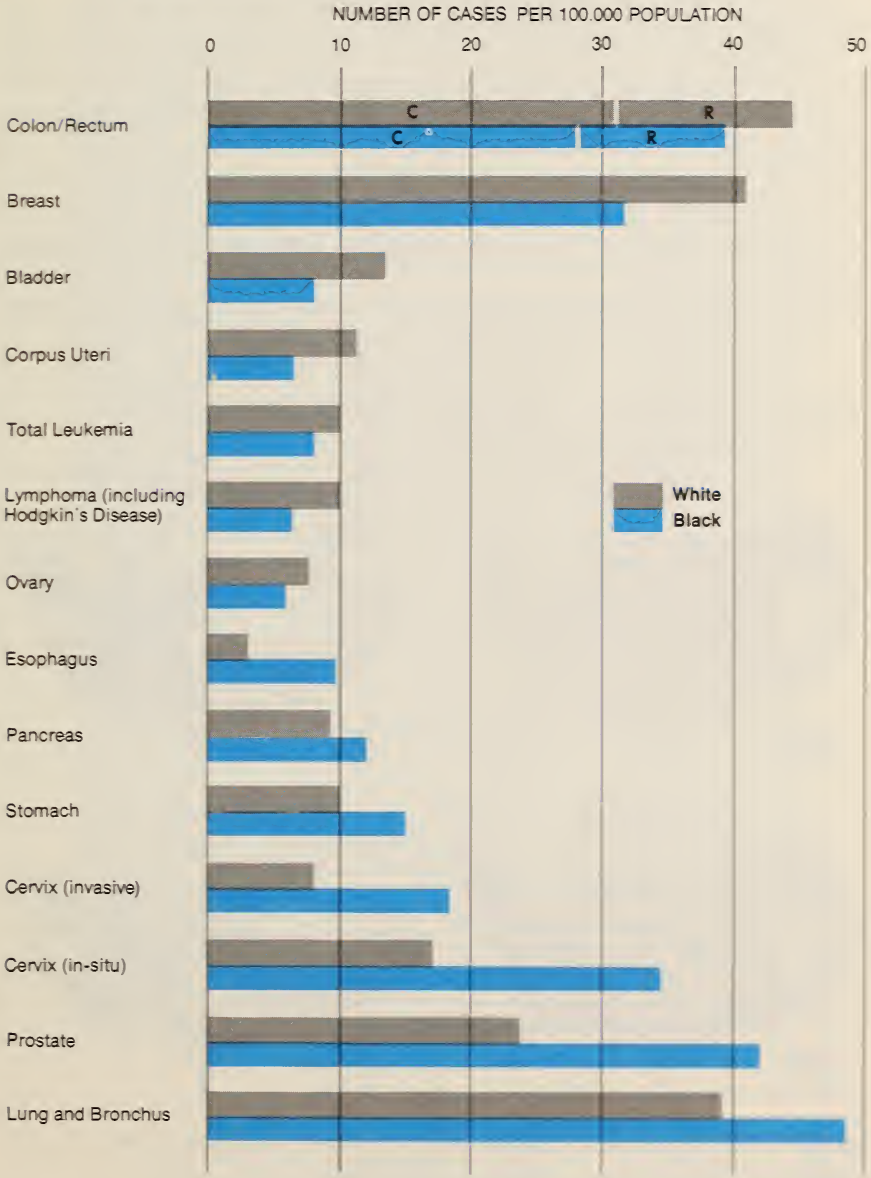
Source: [4, 11]

ovary. Blacks have higher rates for cancers of the esophagus, pancreas, stomach, uterine cervix (both invasive and in-situ), prostate, and lung and bronchus.

The rapid rise in reported mortality for blacks is partially a reflection of improvement in diagnosis and medical care which permit

more accurate certification of cause of death. Other evidence suggests that part of the rise is real and may be related to exposure to

FIGURE 8. CANCER INCIDENCE BY SITE AND RACE: United States, 1969-1971 (age-adjusted to 1970 U. S. population).



Source: [11]

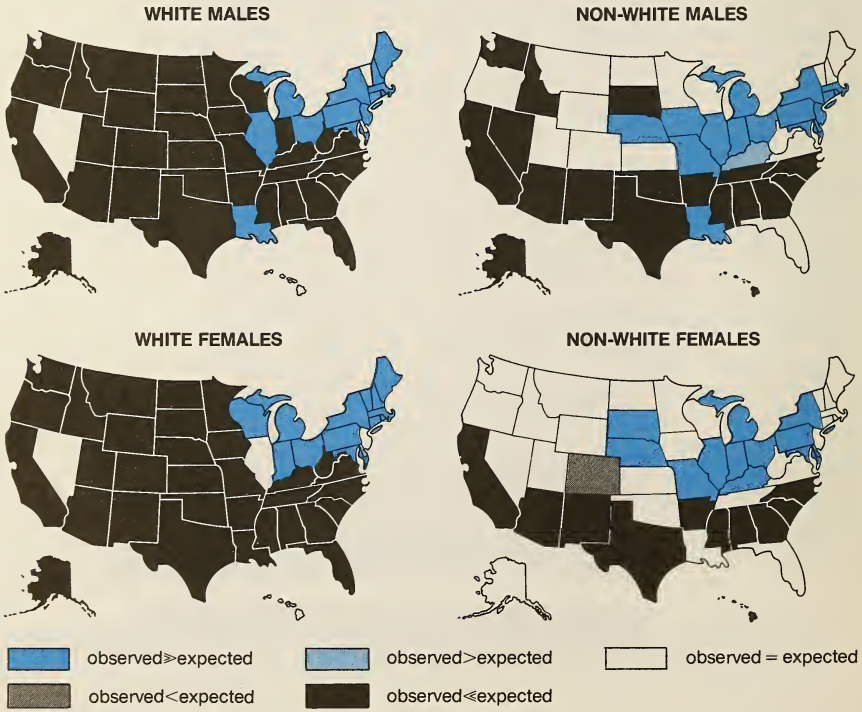
higher levels of industrial and environmental pollutants associated with changes in occupation and life style.

References: [11, 28, 36, 91]

12. Are there regional differences in cancer rates within the United States?

Reported cancer mortality data do show differences from one area to another within the United States. These patterns are different for race-sex groupings. Figure 9 shows race and sex specific cancer mortality patterns for the period 1950 to 1968. For whites (male and female), the United States is essentially divided into 2 regions: The Northeast and Great Lakes states with higher death rates, and the remainder of the country with lower death rates. For male nonwhites, a belt of states with higher rates runs from Nebraska through Massachusetts and lower rates are present throughout the southern third of the country. Female nonwhites have higher rates in the Northeast,

FIGURE 9. GEOGRAPHIC DISTRIBUTION OF CANCER BY RACE AND SEX: United States, 1950-1968.



Source: [2]

TABLE 7. CANCER INCIDENCE RATES* FOR THE AREAS COVERED BY THE THIRD NATIONAL CANCER SURVEY, BY SITE, RACE, AND SEX: United States, 1969-1971.

	ALL SURVEY AREAS	ATLANTA	BIRMINGHAM	COLORADO	DALLAS FT. WORTH	DETROIT	IOWA	MINNEAPOLIS ST. PAUL	PITTSBURGH	SAN FRANCISCO OAKLAND
ALL SITES†										
All Races, Both Sexes	300.0	285.7	274.7	272.6	301.0	303.8	283.3	313.8	298.1	329.8
All Races, Male	346.8	343.9	330.0	310.0	366.4	350.6	319.6	361.3	345.0	371.7
All Races, Female	270.2	253.5	238.3	248.3	259.5	270.2	259.8	288.8	265.1	306.7
White, Both Sexes	297.7	286.5	273.7	267.8	297.8	300.8	282.7	310.6	294.2	332.7
White, Male	342.6	340.2	331.1	305.2	360.4	343.1	318.6	358.5	339.4	375.4
White, Female	270.3	259.1	238.2	243.6	259.5	271.9	259.5	285.6	263.3	311.7
Black, Both Sexes	319.0	282.2	279.6	339.0	327.0	326.5	336.1	363.3	351.2	319.4
Black, Male	397.2	363.2	332.3	445.1	418.0	400.4	408.1	412.0	426.2	402.6
Black, Female	256.8	230.3	239.3	267.5	254.3	263.4	272.6	325.8	281.6	254.5
ALL RACES, BOTH SEXES										
All Sites†	300.0	285.7	274.7	272.6	301.0	303.8	283.3	313.8	298.1	329.8
Esophagus	3.4	4.2	3.1	2.0	3.2	4.2	2.2	3.2	3.8	4.2
Stomach	10.5	7.7	8.8	8.3	8.1	11.9	8.9	11.0	12.5	12.3
Colon	30.9	28.2	24.3	26.5	26.4	31.1	32.6	35.6	32.0	32.9
Rectum	13.6	9.4	8.7	10.0	11.9	14.8	13.4	14.8	15.7	15.4
Pancreas	9.7	9.0	10.2	9.4	10.4	10.1	8.4	9.7	9.4	10.6
Lung & Bronchus	40.0	40.6	43.9	30.8	46.1	42.7	33.4	34.2	41.7	45.0
Breast	40.4	39.1	32.9	38.6	37.5	39.3	39.5	45.4	38.9	45.8
Cervix (Invasive)	8.9	10.2	14.8	7.1	10.5	9.6	8.8	8.8	7.9	7.4
Corpus Uterii	11.0	9.3	7.4	9.8	8.9	11.5	10.1	11.7	10.5	14.7
Ovary	7.6	7.6	5.6	7.5	7.6	7.2	7.9	8.9	7.1	7.9
Prostrate	25.2	25.6	26.6	29.7	24.5	24.9	23.7	27.4	21.3	25.7
Bladder	13.2	9.5	9.4	14.2	10.3	14.2	12.6	13.3	14.7	14.2

*Rates are cases/100,000 population, age-adjusted to U. S. 1970 standard. †"All Sites" excludes skin and carcinoma-in-situ.
Source: [11]

Great Lakes, and Midwest states and lower rates in the southern third of the country.

The above patterns are those for all sites of cancer combined. However, each specific site has its own pattern; for example: cancer of the uterine cervix among nonwhite females shows high mortality rates in the South and skin cancer among whites increases as one moves southward through the country.

For the most part, the states with increased rates are industrial states; a county by county analysis reveals that the areas of high mortality are located in the large cities. For example, the high mortality rates in Illinois are a reflection of high mortality in the Chicago area.

Table 7 presents incidence figures from the Third National Cancer Survey by site, race, and sex, for each of the areas covered by the survey. For all race-sex-sites combined, the highest rates were found in San Francisco-Oakland, Minneapolis-St. Paul, and Detroit; the lowest rates were reported from Colorado, Birmingham, and Iowa. Other patterns are seen for specific tumor sites, and for other race-sex combinations.

References: [2, 9, 11]

13. What are the urban-rural differences in cancer?

It has long been known that densely populated and industrialized areas have higher mortality rates for many causes of death than nearby rural areas. An association between urbanization and mortality has been found for heart disease, cancer of the respiratory and digestive systems, and many other diseases, but the reasons are not fully understood. This urban-rural difference results partly from self-selection and errors in reporting place of residence—many people who become seriously ill move to cities where they can obtain better medical and hospital care, find less demanding occupations, and lead more sedentary lives.

Even when allowance is made for these factors, there remain higher mortality rates for many causes of death, including cancer. This excess risk may be related to life-style (urban dwellers use more tobacco and alcohol), to occupation (working with industrial pollutants), to the environment of the cities themselves (air and water pollution, etc.), or to other factors not yet identified.

References: [46]

14. What are the major histologic types of cancer?

Most body structures are composed of tissues made up of many different types of cells—muscle, connective tissue, glands, blood and lymphatic vessels, etc. Any one of these different cell forms may

TABLE 8. FREQUENCY DISTRIBUTION OF HISTOLOGIC TYPES IN SOME MAJOR SITES OF CANCER: United States, 1969-1971 (TNCS, microscopically proven cases only).

SITE	HISTOLOGIC TYPE	PERCENT
Lung, Bronchus, & Trachea (20,255 cases)	Epidermoid Carcinoma	34.7
	Adenocarcinoma	16.5
	Oat Cell Carcinoma	13.4
	Bronchiolar Carcinoma	3.2
	Other & Unspecified Carcinomas	29.9
	Sarcomas & Lymphomas	0.4
	Other & Unspecified Cancer	1.8
Breast (23,630 cases)	Duct Carcinoma & Paget's Disease	51.0
	Adenocarcinomas	38.6
	Medullary Carcinoma	3.5
	Lobular Carcinoma	2.8
	Colloid Carcinoma	2.2
	Other Specific Carcinomas	1.3
	Stromal Sarcomas & Lymphomas	0.4
	Other & Unspecified Cancer	0.2
Colon & Rectum (24,430 cases)	Adenocarcinomas	87.0
	Colloid Carcinomas	7.8
	Papillary Carcinoma	2.2
	Squamous Cell Carcinomas	1.6
	Other Specific Carcinomas	0.1
	Malignant Carcinoids	0.5
	Sarcomas & Lymphomas	0.4
	Other & Unspecified Cancers	0.4
Stomach (5,085 cases)	Adenocarcinomas	70.9
	Mucinous Carcinomas	6.6
	Signet Ring Carcinomas	1.3
	Other & Unspecified Carcinomas	12.8
	Leiomyosarcoma	1.9
	Lymphosarcoma	1.9
	Reticulum Cell Sarcoma	2.5
	Other & Unspecified Lymphomas	1.0
	Other & Unspecified Cancer	0.9
Prostate (13,206 cases)	Adenosarcomas	98.6
	Medullary Carcinoma	0.3
	Transitional &/or Squamous Cell	0.3
	Clear Cell Carcinoma	0.2
	Other Specific Carcinomas	0.4
	Sarcomas & Lymphomas	0.1
	Other & Unspecified Cancer	0.2
Uterine Cervix (5,169 cases)	Epidermoid Carcinoma	84.1
	Adenocarcinoma	6.1
	Other & Unspecified Carcinomas	9.1
	Sarcomas	0.7
Uterine Corpus (6,593 cases)	Adenocarcinomas	79.5
	Papillary Adenocarcinoma	6.4
	Adenocanthomas	7.6
	Other & Unspecified Carcinomas	2.9
	Mixed Mullerian Tumors	1.5
	Leiomyosarcoma	0.9
	Stromal Sarcoma	0.7
	Other Sarcomas	0.5
	Unspecified Cancer	0.2

Source: [11]

give rise to cancer. Cancers arising from the connective tissue (including bones) are called sarcomas; cancers of the blood-forming system (leukemia, lymphoma) are related to sarcomas. Cancers arising from cells which line the body's internal and external surfaces are called carcinomas; these are further divided into adenocarcinomas (arising from glandular structures), squamous cell carcinomas (arising from skin and other non-glandular surfaces), basal cell carcinomas, and transitional forms. The cell type of a tumor may provide information on its probable etiology and is an important consideration in determining proper therapy and probable outcome (prognosis) of the disease.

The proportion of cases of various histologic types varies widely with site. Table 8 shows the distribution of histology for various major sites. The picture of cancer distribution by histologic type is partially obscured by the cases that are not examined microscopically or not fully classified.

References: [11]

SECTION

2

international distribution of various forms of cancer

International Distribution of Various Forms of Cancer

15. How does the frequency of cancer differ among various countries?

A wide range in frequency of cancer is found among different populations, although no one race or geographical area is completely free of any particular type of cancer (figure 10 and table 9).

International comparisons of cancer mortality among the United States and 23 other countries of Western Europe, Canada, Australia, Chile, and New Zealand show many similarities, but they also show some differences. For all cancer sites combined, white men and women in the United States have below average rates of cancer mortality, but nonwhite men and women have above average rates.

The statistics for most other areas of the world do not allow precise conclusions. However, we know that the total number of cancer deaths must be low in much of Asia and Latin America, simply because the relatively high mortality from diseases of infancy and childhood results in a small proportion of the population surviving to ages of high cancer risk.

In most countries, mortality for males substantially exceeds that for females (table 9). Male-female differences are especially large in Finland, France, Scotland, and England and Wales. Cancer mortality among males is currently rising in nearly all countries, primarily as a result of the world-wide increase in lung cancer, while mortality among females has declined in the majority of counties. The high rates of cancer in males are corroborated by incidence data assembled by cancer registries in the United States, the Scandinavian countries, England and Wales, New Zealand, and elsewhere.

References: [10, 12]

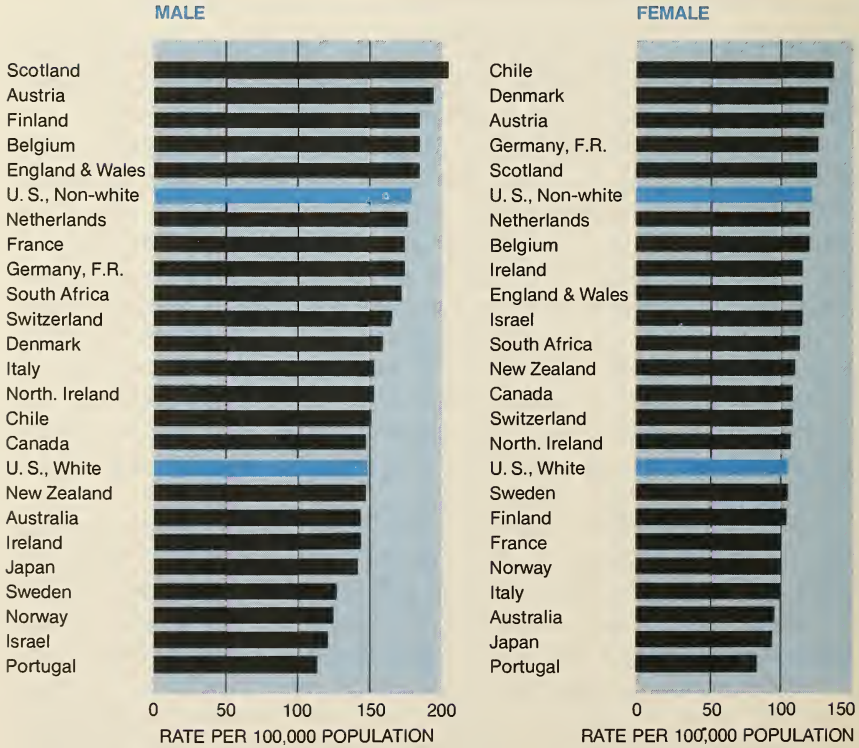
16. How does the distribution of cancer by site vary from one country to another?

Table 10 summarizes international variations in cancer incidence and mortality by site. Differences for some important sites of cancer are discussed in the following questions.

17. How do cancer mortality rates for migrants to the United States compare with rates in their countries of origin?

Differences in cancer mortality among the various foreign-born segments of the United States population were first noted more than

FIGURE 10. AGE-ADJUSTED MORTALITY RATES FOR ALL MALIGNANT NEOPLASMS (including neoplasms of lymphatic and haematopoietic tissues) IN VARIOUS COUNTRIES, 1966-1967.*



*Standard population for this and following similar figures: total male and female population in 46 countries around 1950.

Source: [10]

TABLE 9. AGE-ADJUSTED CANCER MORTALITY RATES IN VARIOUS COUNTRIES, BY SEX, 1956-57 AND 1966-67, WITH MALE-FEMALE RATIOS AND PERCENT CHANGE.

COUNTRY	MALE			FEMALE			MALE-FEMALE RATIO	
	1956-57	1966-67	PERCENT CHANGE	1956-57	1966-67	PERCENT CHANGE	1956-57	1966-67
Australia	130.9	143.2	+ 9	100.4	96.8	− 4	1.30	1.48
Austria	187.6	192.7	+ 3	136.9	130.3	− 5	1.37	1.48
Belgium	153.2	182.9	+19	122.9	120.3	− 2	1.25	1.52
Canada	133.9	146.8	+10	114.4	109.0	− 5	1.17	1.35
Chile	147.0	149.8	+ 2	138.4	137.1	− 1	1.06	1.09
Denmark	152.6	158.2	+ 4	141.6	132.6	− 6	1.08	1.19
England and Wales	170.9	182.5	+ 7	113.4	114.9	+ 1	1.51	1.59
Finland	186.7	183.1	− 2	116.2	102.8	−12	1.61	1.78
France	155.1	174.1	+12	105.9	100.3	− 5	1.46	1.74
Germany, Federal Republic	160.0	174.1	+ 9	128.7	126.5	− 2	1.24	1.38
Ireland	131.4	142.9	+ 9	110.6	115.1	+ 4	1.19	1.24
Israel	116.0	121.5	+ 5	116.7	114.5	− 2	0.99	1.06
Italy	130.6	152.0	+16	99.7	99.3	0	1.31	1.53
Japan	127.6	141.3	+11	94.0	94.9	+ 1	1.36	1.49
Netherlands	148.5	175.5	+18	122.2	120.7	− 1	1.22	1.45
New Zealand	137.4	146.2	+ 6	107.5	109.5	+ 2	1.28	1.34
Northern Ireland	149.4	151.3	+ 1	114.5	107.0	− 7	1.30	1.41
Norway	124.9	124.7	0	106.5	100.1	− 6	1.17	1.25
Portugal	93.1	113.6	+22	75.9	84.4	+11	1.23	1.35
Scotland	183.2	202.8	+11	127.8	124.6	− 3	1.43	1.63
Sweden	119.9	126.1	+ 5	109.2	104.5	− 4	1.10	1.21
Switzerland	182.5	164.4	−10	127.6	107.6	−16	1.43	1.53
South Africa	158.0	171.0	+ 8	117.2	113.4	− 3	1.35	1.51
United States, white	139.6	146.8	+ 5	111.1	104.6	− 6	1.26	1.40
United States, nonwhite	151.1	178.5	+18	125.9	121.9	− 3	1.20	1.46

SOURCE: [10]

TABLE 10. SUMMARY OF INTERNATIONAL COMPARISONS OF HIGH AND LOW RATES FOR CERTAIN SITES OF CANCER, MORTALITY AND INCIDENCE.

COUNTRY	MORTALITY FROM CANCER, COMPARED WITH CANCER MORTALITY FOR UNITED STATES WHITES	INCIDENCE OF CANCER, COMPARED WITH CANCER INCIDENCE IN THE UNITED STATES (CONNECTICUT REGISTRY*)
Austria	high rates for stomach, lung (males), and uterus; low rates for breast, intestine (females), rectum	
Canada	somewhat higher rate for stomach and a moderately lower rate for lung (males)	Alberta registry: lower for lung, intestine, rectum, breast, prostate
Chile	very high rate for stomach; high rate for uterus; low rates for lung (males), breast, rectum, prostate, intestine	
Denmark	moderately high rates for stomach, uterus, ovary, rectum	higher for stomach, uterus; lower for lung (males), intestine, breast, prostate
England and Wales	very high rate for lung and moderately high rates for stomach and rectum	higher for stomach, lung; lower for intestine, rectum, breast, prostate
Finland	very high rates for stomach and esophagus; high rate for lung (males); low rates for intestine, breast	higher for stomach, lung (males); lower for lung (females), intestine, rectum, uterus, breast
Germany	high rates for stomach, rectum; low rates for intestine, breast	higher for stomach, lung (males), uterus; lower for intestine, rectum (males), breast
Ireland	moderately high rate for stomach; low rate for lung (males)	
Israel	higher for stomach; low rates for intestine, rectum (males), lung (males), prostate, uterus	Jews: higher for stomach; lower for lung (males), intestine, rectum, breast, prostate, ovary
Italy	high rate for stomach; low rates for intestine, lung (males), prostate, breast, ovary	
Japan	very high rate for stomach; low rate for intestine; very low rates for lung (males), prostate, breast, ovary	Miyagi prefecture: higher for stomach; lower for lung (males), intestine, rectum, breast, prostate, ovary
New Zealand	higher rates for stomach, rectum (females)	higher for stomach, prostate; lower for lung, intestine, breast

*Almost all cases in the Connecticut registry are whites.

TABLE 10. *Continued*

COUNTRY	MORTALITY FROM CANCER, COMPARED WITH CANCER MORTALITY FOR UNITED STATES WHITES	INCIDENCE OF CANCER, COMPARED WITH CANCER INCIDENCE IN THE UNITED STATES (CONNECTICUT REGISTRY*)
Norway	high rates for stomach, prostate, ovary; low rates for intestine, lung, breast	higher for stomach; lower for lung, intestine, rectum, uterus, breast
Portugal	higher rate for stomach; lower rates for lung, breast, prostate, intestine, rectum (males)	
Scotland	very high rate for lung; moderately high rates for stomach, rectum	higher for stomach, lung; lower for intestine, rectum, uterus, breast, prostate
Sweden	moderately high rates for stomach, ovary, prostate; lower rates for intestine, lung (males), breast	higher for stomach, uterus, ovary; lower for lung, intestine, rectum, breast

Source: [1, 10, 12]

60 years ago. Recent findings on cancer mortality among various migrant groups are contrasted with similar data for the native-born white population of the United States in table 11 and with data from the countries of origin in table 12. These tables present only the more definitive differences seen.

For cancer of the esophagus among males, and to a lesser degree for cancer of the buccal cavity among males, the rates for migrants are usually higher than either those for the population in the country of origin or those for the United States native-born population. For cancer of the stomach the rates for migrants more closely resemble the experience of the country of origin than that of the host United States white population, while the reverse tendency holds true for the large bowel. Observations for persons migrating to Australia after World War II generally agree with the findings described above.

Numerous factors complicate the interpretation of the findings on migrant populations, including variations in the quality of medical care and death certification, selective migration of persons in good or poor health, differences in socioeconomic class distribution, and urban and rural residence patterns. For example, the high mortality from cancer of the esophagus among migrant males seems partly due to the fact that most migrants live in urban areas, where high mortality from this cancer prevails even among the native born. Nevertheless, the data on cancer mortality among migrants strongly

TABLE 11. CANCER MORTALITY OF MIGRANTS TO THE UNITED STATES COMPARED WITH U. S. NATIVE-BORN WHITES.

SITE	LARGE EXCESS RISK AMONG MIGRANTS	LARGE DEFICIT IN RISK AMONG MIGRANTS
Buccal cavity and pharynx	Finland (females) Ireland Sweden (females)	Jews from several European countries including U.S.S.R.
Esophagus	Austria (males) Czechoslovakia Finland (females) Hungary (males) Ireland Poland United Kingdom (females) U.S.S.R. (females)	
Stomach	Austria Czechoslovakia Finland Germany (females) Ireland Japan Mexico (females) Norway Poland Sweden U.S.S.R. Yugoslavia	Italy
Intestines	Ireland (males)	Mexico
Rectum	Ireland (males) U.S.S.R. (males)	Mexico
Bronchus, lung, and trachea	Ireland (females) Mexico (females) Poland U.S.S.R.	
Female breast		Italy Japan Mexico Poland
Cervix uteri	Mexico	Finland Sweden U.S.S.R.
Bladder		Czechoslovakia (females) Italy (females) Poland (females) Sweden (females)
Leukemias and lymphomas	U.S.S.R.	

Source: [78, 113]

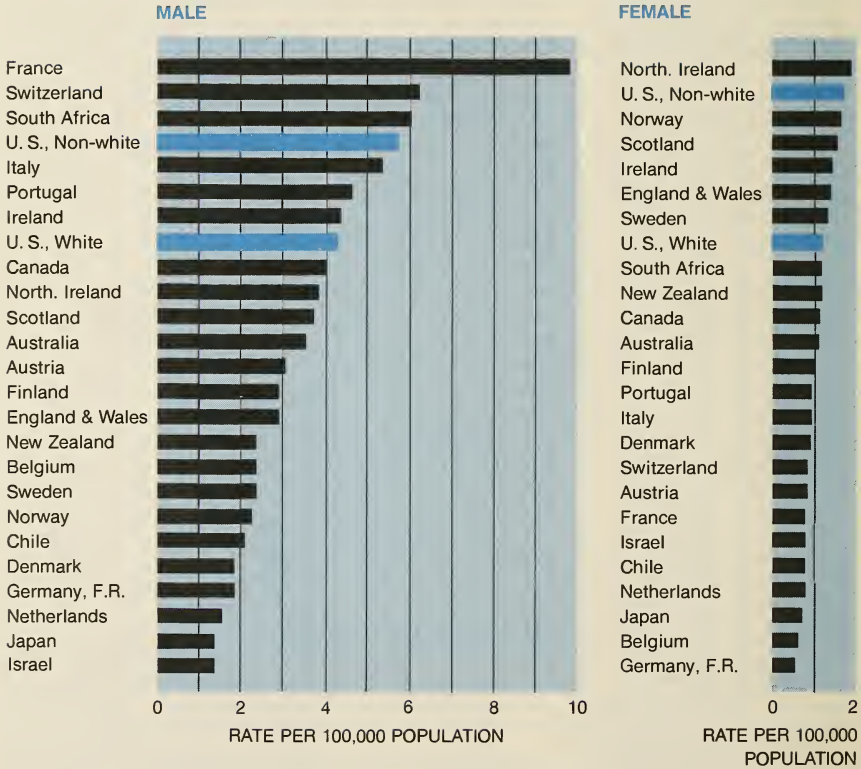
TABLE 12. CANCER MORTALITY OF MIGRANTS TO THE UNITED STATES COMPARED WITH COUNTRY OF ORIGIN.

SITE	LARGE EXCESS RISK AMONG MIGRANTS	LARGE DEFICIT IN RISK AMONG MIGRANTS
Buccal cavity and pharynx	Canada (males) Finland (females) Germany (males) Ireland (males) Mexico	England and Wales (females)
Esophagus	Hungary (males) Ireland (males) Italy (males) Mexico (males) Norway (males)	
Intestines	Czechoslovakia Hungary (males) Ireland (males) Italy (males) Mexico Poland	
Rectum	Italy (males) Mexico Poland	
Lung, bronchus, and trachea	Italy (males) Mexico Norway (females) Poland Sweden (males)	England and Wales
Prostate	Ireland Japan Poland	
Female breast	Poland	
Cervix	Italy Mexico	Sweden
Uterus, except cervix		Austria Hungary Italy Mexico
Ovary	Ireland Italy Japan	
Leukemias	Austria Mexico Poland (males) Yugoslovia (males)	

Source: [78, 113]

support the presumption of true differences in risk for specific sites not only among countries, as revealed by the available international comparisons, but among population groups within the United States as well. The data for most sites, showing changes among migrants from rates in their native countries to those of their host countries, support the hypothesis that many cancers are largely environmental in origin.

FIGURE 11. AGE-ADJUSTED MORTALITY RATES FOR MALIGNANT NEOPLASMS OF THE BUCCAL CAVITY AND PHARYNX IN VARIOUS COUNTRIES, 1966-1967.



Source: [10]

Detailed studies of migrant groups may be helpful in further assessing the relative contributions of environmental agents and host characteristics in the etiology of individual sites of cancer. Studies of cancers of the stomach and large bowel among the Japanese migrants in Hawaii are now in progress.

References: [78, 113, 120, 163]

18. What are some important epidemiologic features of cancer of the buccal cavity and pharynx?

Mortality rates for cancer of the buccal cavity and pharynx vary substantially from one population to another (figure 11). Furthermore, the data on all forms of buccal and pharyngeal cancer combined may mask additional variations in risk for specific tumor sites. For instance, in the United States a rise in pharyngeal cancer mortality among white males has been overbalanced by a decline in mortality from cancer in various parts of the mouth; thus mortality from these cancers declined slightly in the white population of the United States over the last 40 years, while there was a small increase for nonwhite females and mortality rates for nonwhite males doubled. Part or all of this increase among nonwhites may have been due to improved certification of cause of death. Mortality among females in England and Wales, Canada, and Australia has remained almost constant, although rates for males have decreased in each of these countries. Incidence in the United States has been stable over the last 30-40 years.

Nasopharyngeal cancer is relatively rare in North Americans and Europeans, but is common in Chinese, Malays, Indonesians, and Thais. In studies of Chinese in Singapore and Hong Kong, rates were higher for Chinese with family origins in South China (Kwangtung) and lower for those from North China (Chekiang, Fukien, Kiangsu). There is some evidence of a decreased risk of nasopharyngeal cancer for Chinese born in the United States. These findings suggest a genetic susceptibility to an environmental carcinogen. A number of possible etiologic agents have been suggested including hot food, alcohol, tobacco, opium smoking, and wood or kerosene smoke in poorly ventilated houses. Recent work has focused on a possible link with Herpes viruses.

In patients with intraoral cancer, tobacco use (any form) and alcohol consumption are more common than in controls, and the effects of the two agents may be synergistic. In India, where oral cancer rates are high, chewing of tobacco and betel has been implicated as an etiologic factor. Other possible risk factors for intraoral cancers include syphilis (for cancer of the tongue), Plummer-Vinson syndrome, B-vitamin deficiency, and radiation (at therapeutic, not diagnostic levels). There is no definitive evidence that chronic irritation from ill-fitting dentures or from the consumption of hot and spicy food contribute to increased risk.

References: 13, 67, 90, 104, 110, 134, 139, 143, 146, 154, 157, 159, 181

19. What are some important epidemiologic features of esophageal cancer?

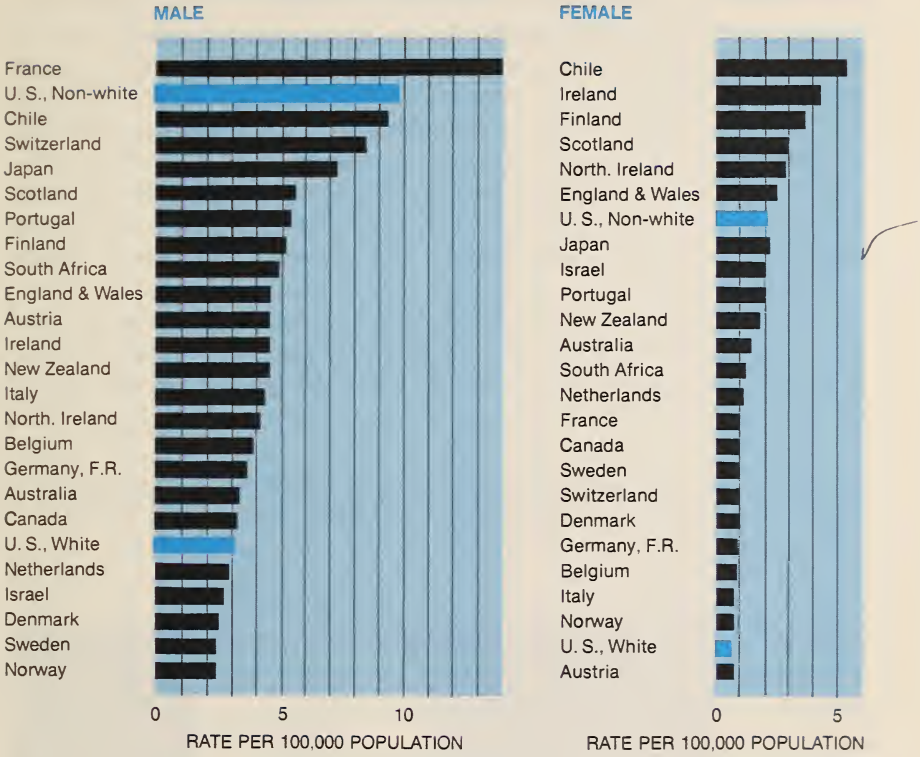
Reported mortality rates for esophageal cancer show remarkable variation, even between adjacent countries (figure 12), and the high degree of geographic variation in the male/female ratio is characteristic of this cancer. For instance, males in France and Switzerland experience high mortality, but females have below average rates; in Ireland and Scotland, it is the females who display the high rates. Some parallels in the patterns of international variations in mortality for cancers of the esophagus (figure 12) and buccal cavity and pharynx (figure 11) may be noted.

In the United States, incidence and mortality for blacks are currently much higher than for whites, the difference in incidence being more than 2-fold for females and more than 3-fold for males. Further, since 1940 incidence rates have rapidly increased for U.S. blacks, particularly for males, whereas rates for the whites have shown a slight decline. A rapid increase for blacks has been reported for Bantus in the Transkei (South Africa) as well, suggesting the recent introduction of an etiologic agent.

There are several nonwhite populations outside the United States which have extremely high death rates from esophageal cancer, while neighboring areas are relatively free from the disease. Esophageal cancer is the most frequent malignant neoplasm in the native population of Curacao, but is comparatively infrequent in Cuba, Jamaica, and Venezuela. Rates are higher in the north of China than in the south. The incidence of cancer of the esophagus among Bantu males in South Africa is very high by Western European standards, but the available data do not indicate high rates among Africans living in neighboring Mozambique. In Central and East Africa areas of high and low incidence are found in close proximity. In a small area along the Caspian littoral, a geographic gradient in incidence has been described which correlates well with rainfall and soil conditions. In the United States, adjacent counties may have significantly different rates. There is general agreement that esophageal cancer is significantly more common in urban areas than in adjacent rural areas. In some countries, incidence or mortality rates are higher in low income groups than among the well-to-do. (See also Question 31.)

Genetically similar groups that are geographically widely separated show differences in incidence. For instance, the Indians of Natal, South Africa, have a lower rate than Indians in Bombay; blacks of West Africa have a lower rate than United States blacks (75 percent of American blacks are descended from West Africans). Environmental factors are probably responsible for such differences in risk.

FIGURE 12. AGE-ADJUSTED MORTALITY RATES FOR MALIGNANT NEOPLASMS OF THE ESOPHAGUS IN VARIOUS COUNTRIES, 1966-1967.



Source: [10]

Some factors that have been considered as possible etiologic agents include the use of alcohol and tobacco, consumption of hot foods and liquids, heavy seasoning of foods, chewing betel nut, Plummer-Vinson syndome, radiation (in quarries, in soils, and in houses), exposure to asbestos, air pollution, factors in water supply and soil (including trace metal deficiencies and alkalinity), vitamin C deficiency, contamination of food with silica particles, and consumption of tannin-rich foods.

References: [8, 9, 12, 33, 41, 56, 95, 114, 129, 145, 154]

20. What are some important epidemiologic features of stomach cancer?

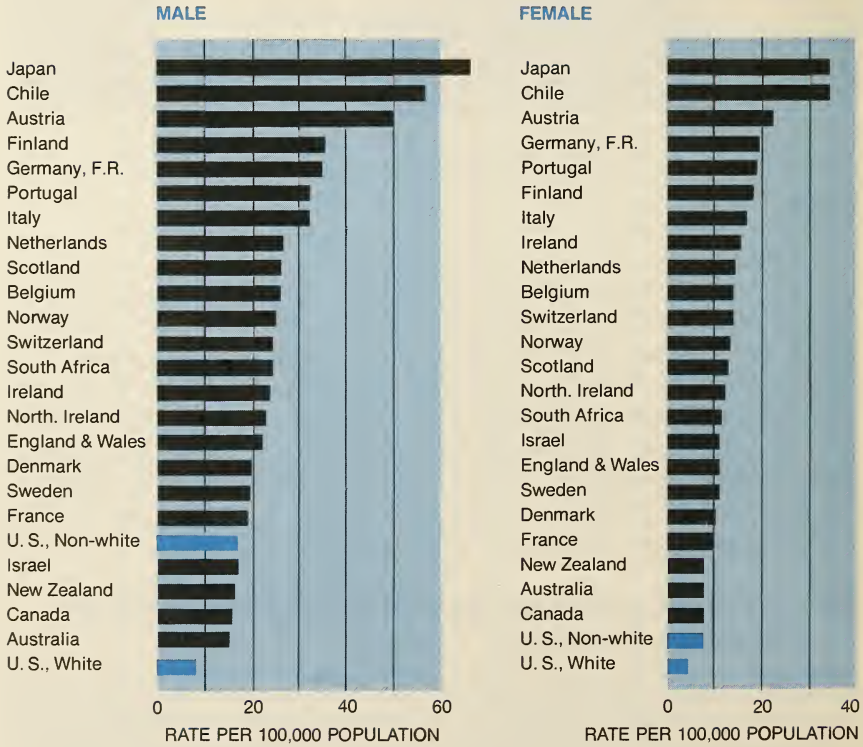
Incidence and mortality rates for stomach cancer have been decreasing for several decades in the United States. Evidence for a decline has more recently been seen in several other countries. Japan, which has one of the highest rates in the world, shows no

evidence of a decline among males and only a suggestion of one among females.

Figure 13 describes mortality from stomach cancer. Only fragmentary data are available for persons living in non-Western environments. In Chile the rate is high, but in other parts of Latin America, and also in Mozambique, Java, and among South African Bantus, relatively low risks of stomach cancer have been reported. Migrants to the United States from high-risk populations generally show rates only slightly lower than their country of origin. Many countries report higher rates among lower socioeconomic classes, especially among certain occupational groups (for example coal miners and textile workers).

Of the two major histologic types of adenocarcinoma of the stomach, most characteristics of this disease seem related to the so-called "*intestinal*" type rather than the "*diffuse*" type. The risk of

FIGURE 13. AGE-ADJUSTED MORTALITY RATES FOR MALIGNANT NEOPLASMS OF THE STOMACH IN VARIOUS COUNTRIES, 1966-1967.



Source: [10]

the intestinal type rises in males after age 40, causing a rise in the male/female ratio from close to one at young ages to almost two at ages 55-60; the ratio thereafter declines as rates for females begin to rise. Intestinal metaplasia of the stomach may represent a precursor of the intestinal type of cancer; this metaplasia may be irreversibly established at an early age by an environmental agent. This could account for the continued high liability of gastric cancer observed in migrants from high to low risk countries. The decline in stomach cancer that has been observed among Japanese migrants to Hawaii and their offspring has been mostly of the intestinal type.

The reported association between "*diffuse*" carcinoma and blood group A suggests the importance of host related (rather than environmental) factors in the etiology of this type of stomach cancer. A correlation between gastric ulcers and the later development of cancer has often been hypothesized and may be supported by data from Japan. In the United States however, ". . . the association is so uncommon that benign peptic ulcers of the stomach can not be regarded as a precancerous lesion"[165].

Other factors that have been studied for possible associations with stomach cancer include soil type, air pollution, foods (particularly salt and pickled vegetables, and a lack of uncooked vegetables), and endogenous factors such as pernicious anemia, achlorhydria, and low pepsin levels. No significant relationships between stomach cancer and the use of tobacco, alcohol, spices, thoroughness of mastication, rapidity of eating, and the temperature of food have been demonstrated.

References: 4, 26, 50, 52, 62, 76, 77, 80, 86, 95, 118, 128, 136, 144, 156, 165, 166, 180, 184

21. What are some important epidemiologic features of cancer of the large bowel?

Figures 14 and 15 show that Scotland and Denmark have relatively high mortality rates for cancer of both intestine and rectum. Portugal, Israel, and Chile rank low for both sites. Since cancers of the large intestine and rectum arise in similar tissues, it is of interest to note populations with deviant colon/rectum ratios: Austria and Germany rank significantly lower for cancer of the large intestine than for rectal cancer, while the reverse is true for Australia and U.S. whites. Apparent differences in tumor localization within the large bowel may be due in part to anatomical classification practices and the quality of death certifications, but it seems unlikely that these factors could explain all of the differences observed. Furthermore there are differences between cancer of the rectum and of the colon which suggest the possibility of different etiologies for different parts of the large bowel: cancer of the rectum is more common in males than females, but this is not true for the colon; in countries in which

FIGURE 14. AGE-ADJUSTED MORTALITY RATES FOR MALIGNANT NEOPLASMS OF THE INTESTINE (excluding rectum) IN VARIOUS COUNTRIES, 1966-1967.

Source: [10]

large bowel cancer is common the excess is concentrated in the rectum and the left side of the colon, and the male/female ratio is lower; and shifts in localization over time have been observed in Connecticut, particularly for men.

In the United States between 1935-1969, both incidence and mortality rates for black males and females have risen, with greater increases in incidence than in mortality. Mortality and incidence for whites rose during 1935-1947, but since that time only minor changes in incidence and mortality have been noted.

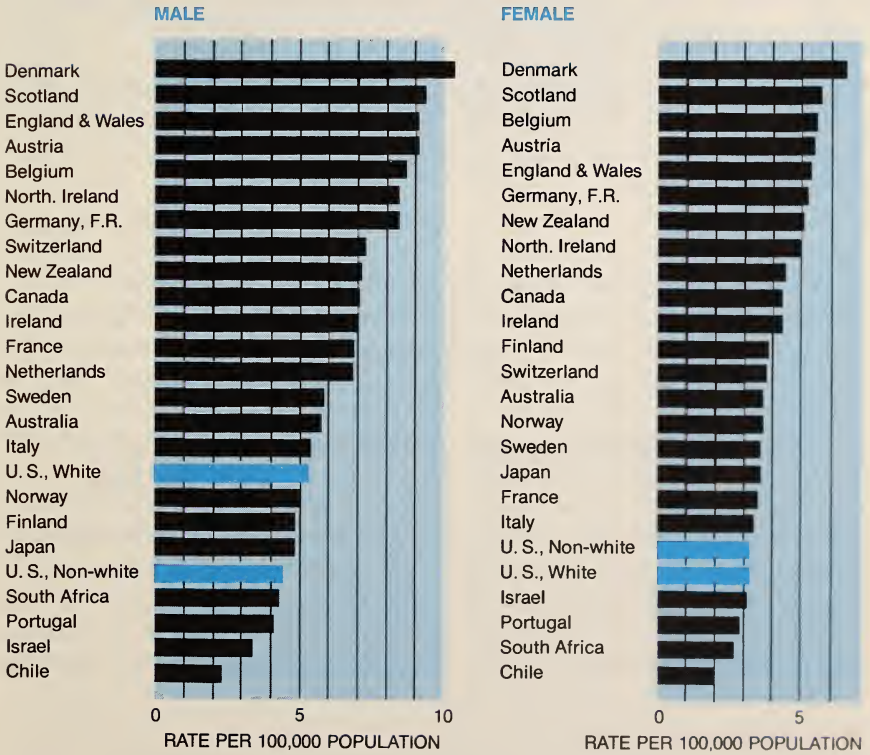
Migrants to the United States from Japan, Norway, and Poland have shown rises in colon cancer rates to the United States level from the low rates of the countries of origin. Rates for rectum also rose for migrants from Norway and Poland, but not for the Japanese, whose rate was already comparable to the United States rate. Japanese in Hawaii have rates comparable to whites. Rates are higher

for Negroes and Chinese living in the United States than in their native countries.

Within the United States, rates of large bowel cancer are higher for urban than rural residents and higher for residents of the Northeast and Northcentral states. Persons who migrate between urban and rural areas adopt the mortality rate of the current place of residence. This is similar to the experience of migrants to the United States. There are no striking social class differences in the developed countries of North America and Western Europe.

Hereditary factors in the genesis of colorectal cancer include such familial diseases as immune globulin deficiencies, Gardner's syndrome, and the familial polyposes. Other conditions predisposing to colorectal cancer include ulcerative colitis, villous adenoma, and possibly Crohn's disease. Excluding these special risk factors, the increased risk in immediate relatives of patients with large bowel

FIGURE 15. AGE-ADJUSTED MORTALITY RATES FOR MALIGNANT NEOPLASMS OF THE RECTUM IN VARIOUS COUNTRIES, 1966-1967.



Source: [10]

cancer is about two or three times normal. (See also Question 28.)

Environmental factors are probably more important than hereditary factors in the genesis of cancer of the large bowel. Diet may be a critical environmental variable. Burkitt has noted the greater frequency of colorectal cancer, diverticulitis, and appendicitis in economically developed areas and remarked on the low fiber and high refined carbohydrate content of the diet in these populations. Such a low fiber diet affects the speed of transit, bulk, and consistency of the stool, and the distribution of intestinal flora. It is known that intestinal flora are capable of metabolizing some compounds into proximate carcinogens which may be held in prolonged contact with the gut because of the decreased motility. A 1973 case-control study has detected a higher consumption of meats, particularly beef, and of legumes among Japanese bowel cancer patients in Hawaii than among controls. Efforts are underway to pinpoint the relationship between diet and factors known to be different in high and low risk areas: the distribution of fecal flora and fecal steroids (metabolized by intestinal bacteria).

References: 21, 33, 37-39, 56, 81-84, 97, 98, 133, 138

22. What are some important epidemiologic features of liver cancer?

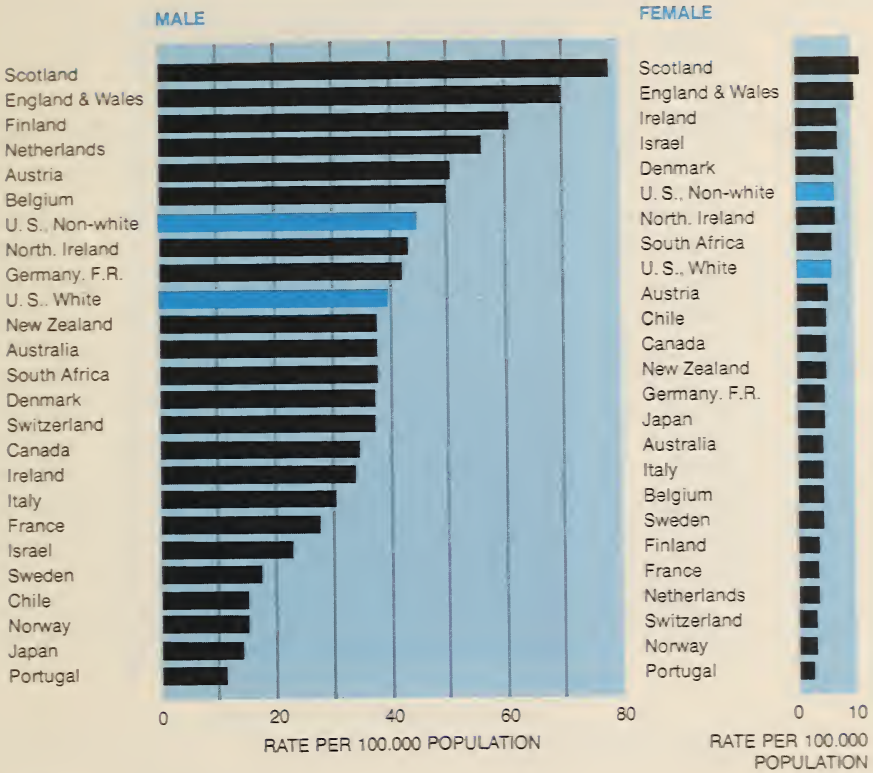
In the United States and most other Western countries, cancer of the liver is relatively uncommon, but in some parts of Africa and Asia it is frequently seen. In most countries the mortality rates are higher for males than females.

In high incidence areas the disease presents at earlier ages and follows a more rapid clinical course. Observed differences in incidence and mortality are probably not due to racial or genetic factors alone. In Singapore, where the incidence is particularly high among the Chinese, liver cancer appears to be more common among migrants from China than among the Singapore-born Chinese. Despite high rates for African blacks, United States blacks have rates similar to whites. Aflatoxins produced by molds growing on food may be partly responsible for the high rates of liver cancer in Africa.

Dietary deficiencies seem to play a role in the occurrence of cancer of the liver. There is an excess of this type of malignancy in areas where chronic malnutrition, particularly serious protein deficiency, is widespread. Conversely, in animal experiments a diet high in protein, riboflavin, amino acids (especially choline and cystine), and copper additives appears to have a protective effect against carcinogenesis.

Portal cirrhosis and hemochromatosis of the liver are often observed in low-incidence areas prior to onset of clinical cancer. Other etiologic factors implicated include alcoholism, parasitic infesta-

FIGURE 16. AGE-ADJUSTED MORTALITY RATES FOR MALIGNANT NEOPLASMS OF THE LUNG, BRONCHUS, AND TRACHEA IN VARIOUS COUNTRIES, 1966-1967.



Source: [10]

tions, serum hepatitis, and presence of Australian antigen; there have been recent reports of possible association between liver tumors and the use of androgenic therapy.

References: [22, 63, 65, 100, 103, 135, 158]

23. What are some important epidemiologic features of lung cancer?

The rise in reported morbidity and mortality from cancer of the lung, trachea, and bronchus in the United States during the past few decades reflects a true increase in risk for this site. Lung cancer is now the leading cause of death from cancer among United States males. Mortality trends in many other countries generally parallel those reported in the United States. Lung cancer mortality in Scotland, England and Wales, and Finland is particularly high (figure 16). Rates for nonwhites in the United States have increased faster than for whites.

FIGURE 17. AGE-ADJUSTED MORTALITY RATES FOR MALIGNANT NEOPLASMS OF THE FEMALE BREAST IN VARIOUS COUNTRIES, 1966-1967.

Source: [10]

Mortality in the U.S. among men is 6 times as high as among women, but in the past decade rates for women have risen faster than for men, leading to a decline in the male-female ratio. This change is believed due to recent increases in smoking among women.

Factors associated with increased risk include low socioeconomic status and urban residence. Occupational groups showing high risk include uranium miners, painters, carpenters, and handlers of chromate, nickel, and asbestos. (See also Question 37.) Some of these occupational groups show increased risk of only one specific histologic type of the disease.

A variety of studies from many countries has consistently indicated that excess risks in mortality and morbidity are particularly associated with cigarette smoking. (See also Question 33.) The dose-response relationship of cigarette smoking and lung cancer is noted for epidermoid and small cell anaplastic carcinoma. Filter smokers may be at less risk; exsmokers show a decreased risk after four

years of nonsmoking. There is some evidence that the risk from smoking and the risk of occupational exposure, such as handling uranium or asbestos are together greater than expected from the two exposures added together.

References: [8, 35, 115, 152, 155, 161, 182, 185]

24. What are some important epidemiologic features of breast cancer in females?

Breast cancer is an important cause of illness and death among females in the United States and many other countries (figure 17), but seldom occurs among males. Although incidence has increased (more for blacks than whites), survival has also increased, so mortality rates have remained almost unchanged during the last four decades. Polish migrants to the United States show an increase in risk of developing breast cancer to the level for United States native whites. Japanese migrants on the other hand have shown the persisting low rates characteristic of Japan, but it is too early for firm conclusions since few second generation Japanese living in America have yet attained the ages of high risk for breast cancer. Breast cancer is relatively uncommon among Chinese living in the United States and among American Indians. These data support the importance of genetic factors but do not rule out environmental factors.

TABLE 13. VARIABLES ASSOCIATED WITH THE RISK OF FEMALE BREAST CANCER.

VARIABLE	RISK OF BREAST CANCER	
	LOWER	HIGHER
Race	Oriental	Caucasian
Caucasian admixture in Negroes	Lesser	Greater
Ethnic group	Gentiles	Jews
Marital status	Married	Single
Age at first pregnancy	Younger	Older
Number of pregnancies	More	Fewer
Age at menarche	Later	Earlier
Artificial menopause	Present	Absent
Benign breast disease	Absent	Present
Family history of breast cancer	Absent	Present
Socioeconomic status	Lower	Higher
Blood group phenotype ss in S antigen system	Absent	Present
Obesity, high intake of butter, cheese, milk, green vegetables, sugar, fat	Absent	Present

Source: [189]

International data uniformly show rising incidence with age up to the time of menopause; after menopause the rate rises more slowly with age or remains constant.

Table 13 lists some of the variables reported in the literature to influence the risk of breast cancer. The findings on unmarried women are reinforced by data on nuns, who have high rates of breast cancer but low rates of cervical cancer. (See also Question 30.) Many of the important variables are genetic and endocrine-related. Approximately a two-fold excess frequency of breast cancer is found among the mothers and sisters of patients with breast cancer. Recent work on endocrine factors has investigated abnormalities in estrogen/androgen ratios in breast cancer patients and found the same abnormalities in their sisters. The protective effect of early first pregnancy may operate through changing the estrogen fraction ratio during a critical period in the life of the woman. Ratios of estriol to estrone plus estradiol are higher in the urine of Asians than in North Americans, who have higher rates of breast cancer. Other hormones may influence breast cancer; for instance, some breast tumors are dependent on prolactin. Research to date has not indicated that oral contraceptives increase the risk of breast cancer.

Viruses related to those causing mouse mammary tumors have been demonstrated in human breast cancers. Clarification of the role of these viruses in human breast cancer awaits further research.

References: [27, 46, 48, 56, 57, 85, 106, 119, 125, 126, 151, 162, 173, 189]

25. What are some important epidemiologic features of cancer of the uterine cervix and corpus?

Study of the epidemiology of uterine cancer is complicated by the fact that the two parts of the uterus, cervix and corpus, display distinctly different patterns of cancer incidence. Unfortunately, a high proportion of medical records, particularly death certificates, fails to specify whether the cervix or corpus is the primary site of the tumor. Most of the unspecified cases are thought to be corpus. International comparisons for all forms of uterine cancer are presented in figure 18.

Reported mortality from cervical cancer over the last twenty years has decreased in the United States and survival for cervical cancer has increased. Although these changes started before the introduction of cytologic screening programs, some researchers feel that these screening programs have increased the detection of in-situ lesions and decreased the incidence of invasive malignancies of the cervix without reducing the incidence of endometrial cancer. A faster decline in mortality is seen for nonwhites, except for the age group over 60 years; rates for that age group have not declined appreciably. Nevertheless, rates for United States nonwhites remain higher than for whites. England and Wales, Scotland, Netherland,

FIGURE 18. AGE-ADJUSTED MORTALITY RATES FOR MALIGNANT NEOPLASMS OF THE UTERUS (all parts) IN VARIOUS COUNTRIES, 1966-1967.

Source: [10]

Denmark, Norway, Switzerland, New Zealand, Japan, and Chile show an overall decline in cervical cancer mortality, but in some of the countries there are some birth-cohorts which have not shown a decline. It has been suggested that the cohort effect results from disturbances in sexual relationships caused by the world wars.

The collective evidence suggests that the primary factors increasing the risk of cervical cancer are associated with coitus rather than with childbearing. Factors reported in the literature to be associated with an increased risk of cervical cancer include early marriage (see also Question 30), promiscuity, multiple and broken marriages, young age at first intercourse, high parity, history of syphilis, low socioeconomic status, and cohabitation with uncircumcised male partners. Jewish women have low rates, but circumcision of male partners is no longer viewed as a sufficient explanation for this phenomenon. Recently, some investigators have reported an excess number of patients to have serological evidence of previous infection by Herpes simplex type II virus, or a history of previous infec-

tion by chlamydia and mycoplasma. Maternal exposure during pregnancy to stilbestrol and related compounds has been associated with carcinoma in the offspring; the major association has been noted with vaginal cancer, but cases of clear-cell adenocarcinoma of the cervix have also been reported.

Factors which have been linked to cancer of the uterine corpus differ from those linked to cervical cancer. They include hypertension, nulliparity, late age of menopause, heavy menses, premenstrual breast swelling, obesity (especially among tall women), diabetes mellitus, thyroid disease, hyperestrogenism and hypoestrogenism, and stilbestrol treatment of gonadal dysgenesis. Increased retention of certain endogenous hormones has been proposed as a mechanism that might account for some of these observations.

References: 16, 19, 32, 42-45, 55, 69, 92, 93, 105, 121, 127, 150, 170, 172, 183

26. What are some important epidemiologic features of prostatic cancer?

Cancer of the prostate is the second most common form of malignant neoplasm among U.S. males. In the United States reported incidence and mortality has risen sharply over the last four decades for blacks, and incidence rose slightly for whites. In most other countries mortality rates have increased. U.S. nonwhites show the highest mortality rates of many countries (figure 19).

Some epidemiologic features of prostatic cancer are the high frequency among male relatives of prostatic cancer patients and its rarity in Orientals, although the incidence of clinically active disease has increased for Japanese migrants to the United States. Viral and hormonal etiologies have been proposed. Male sexual activity (including frequency of extramarital contacts and rate of venereal disease) may be associated with an increased risk. An excess frequency of viral and gram-negative bacterial infections of the prostate has been noted in patients with cancer of the prostate.

References: 17, 56, 109, 164, 179, 187

27. What are some important epidemiologic features of leukemia and lymphoma?

Distinction between leukemia and lymphoma is sometimes difficult because certain forms of these diseases share many clinical and pathological characteristics. However, the two diseases do present some distinctive features.

LEUKEMIA:

Leukemia is distinguished from most other neoplasms by its relatively high frequency among children under 10, uniformly low

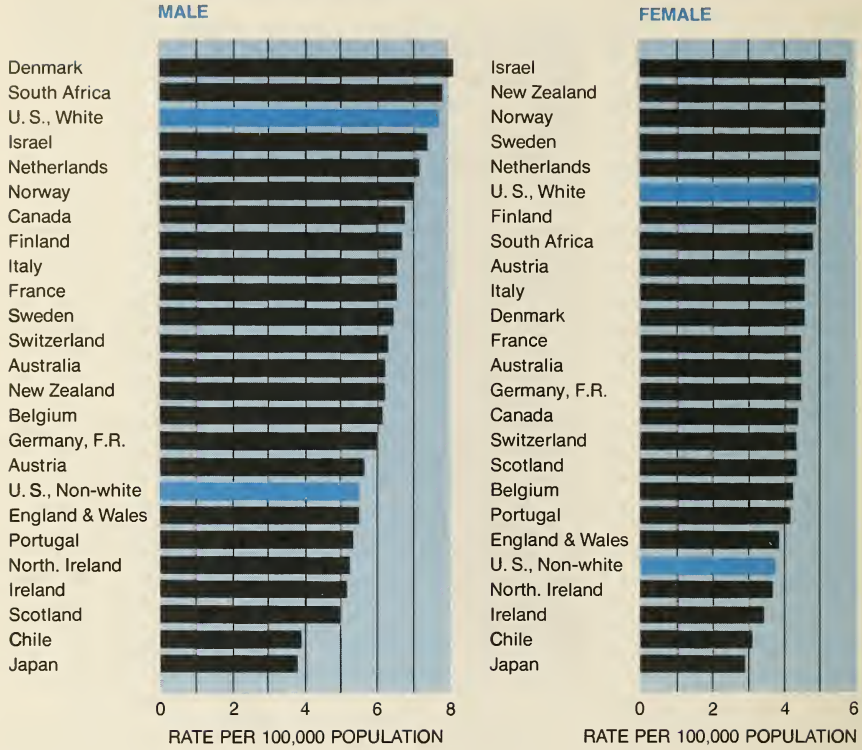
FIGURE 19. AGE-ADJUSTED MORTALITY RATES FOR MALIGNANT NEOPLASMS OF THE PROSTATE IN VARIOUS COUNTRIES, 1966-1967.

Source: [10]

mortality rates in persons ages 10-35, and gradual rise in death rates throughout the remainder of the lifespan. The risk for chronic lymphocytic leukemia shows a higher rise with age than does that for any other form of the disease. A higher male than female mortality is found for leukemia among both whites and nonwhites and at all ages; the male/female ratio is especially high for chronic lymphocytic leukemia (2:1). International variations in mortality rates for leukemia are relatively small compared with those for many other forms of cancer (figure 20), but there are geographic differences: Africans, Indians, and Japanese have lower rates than North Americans, Israelis, and Scandinavians. The low rates in Japan are largely due to a deficit in the lymphatic forms. Acute lymphocytic leukemia is largely a disease of childhood throughout the world.

Reported leukemia mortality in the United States and Great Britain has been rising for at least 40 years. In the United States the increase has been greatest at older ages and among nonwhites, but nonwhites still have mortality rates lower than the white population.

FIGURE 20. AGE-ADJUSTED MORTALITY RATES FOR LEUKEMIA AND ALEUKEMIA IN VARIOUS COUNTRIES, 1966-1967.



Source: [10]

Changes in leukemia mortality and morbidity in the United States have been consistent with trends in most other countries, including England and Wales, Canada, Denmark, and Switzerland. Better diagnosis has probably played some role in the reported increase of this type of malignancy in all these countries, but there has been a genuine increase as well. Age-sex patterns of leukemia incidence are generally similar to those of mortality.

Environmental factors associated with the level of leukemia risk include exposure to certain chemicals (e.g., benzene), radiation (from diagnostic and therapeutic X-rays, atomic bombs, and prenatal X-rays), and urbanization. Host factors include race and heredity, endocrine imbalances, diseases such as Down's, Bloom's, and Fanconi's syndromes, and ataxia-telangiectasia. The risk is increased for sibs of a patient, especially for a monozygotic twin. Down's syndrome may predispose to leukemia through impaired cellular immunity. Reports on space-time clustering have led to a

TABLE 14. EPIDEMIOLOGIC FEATURES OF THREE SUBGROUPS OF HODGKIN'S DISEASE PATIENTS.

VARIABLE	SUBGROUPS, DISTINGUISHED BY AGE AT CLINICAL ONSET		
	0-14 YEARS	15-34 YEARS	50 YEARS AND OVER
Peak age of onset	?	25-29	65-74
Sex ratio (% male)	85%	54%	63%
Race (U.S.A.)	?	Negro rates approximately 75% of white rates	Negro rates approximately 75% of white rates
Religion (New York City)	?	No association	Jews higher than Catholics or Protestants (approximately × 2)
Socioeconomic status (U.K., U.S.A.)	?	Associated with high socioeconomic status (approximately × 2)	Associated with high socioeconomic status (approximately × 2)
Secular trend (U.S.A.)			
Past 40 years	Decline (65%)	Increase (140%)	Increase (110%)
Past 15 years	Decline (20%)	Slight increase (15%)	Constant
Urban:Rural (Denmark)	Rural higher than urban rates	No difference	No difference for males; urban higher for females (?)
International comparison	Reported very high in some areas (e.g., Peru)	More common in Netherlands (× 1.8) Denmark (× 1.5) and 7 other reporting countries than in U.S.; almost absent in Japan	More common in U.S. than any other country reporting mortality; as common in Japan as in some European countries
Familial concentration	?	Small but definite	?

Source: [124]

search for a viral etiologic agent. Viral infection of the mother during gestation has also been suspected as a factor in the subsequent development of leukemia in the offspring.

References: [8, 15, 24, 64, 66, 74, 131, 146, 167]

LYMPHOMAS:

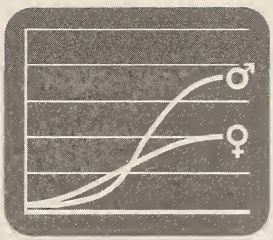
U.S. mortality rates for lymphomas from 1911-1965 have shown increases of 2.5 times for Hodgkin's disease and about 1.7 times for other lymphomas. In Japan, Hodgkin's disease accounts for a smaller proportion of total lymphomas than in the United States and England. Urban dwellers have a higher risk of developing lymphoma than rural dwellers. Transplant recipients have a markedly increased risk of developing lymphoma, particularly reticulum cell sarcoma.

The epidemiology of Hodgkin's disease has received a great deal of attention in the last 15 years. In the United States, Hodgkin's disease is the most common neoplasm of young adults and the most common lymphoma in any age group. The disease shows bimodal age-specific incidence, with peaks in the age ranges 25-29 years and 65-74 years. Many features of the disease are different in the different age ranges. MacMahon distinguished three age ranges: 0-14 (prior to the first peak), 15-34 (the first peak), and over 50 years (the second peak). Table 14 shows some epidemiologic features of these subgroups.

Other comparisons further distinguish the disease in young adults from the disease in older adults. In the southeastern United States, rates are low for the young, but average for the old. Histologic type, localization, and prognosis are more favorable in the young. Histologic type is more favorable in females and in affluent compared to developing countries. Familial and space-time clusterings have been reported, but results of systematic evaluations of clustering have been negative. An increased risk in young patients receiving tonsillectomy has been suggested, but data are conflicting. These observations have suggested that the etiologic agent may be different in young compared to old patients, but differences in host response to the same etiologic agent may account for the epidemiologic differences. An Epstein-Barr virus has been suggested as an etiologic agent. Similarities of Hodgkin's disease are noted with infectious mononucleosis, Burkitt's lymphoma, and Marek's disease of chickens, all of which are associated with Epstein-Barr viruses. Ataxia-telangiectasia and other immune deficiencies may increase the risk of developing Hodgkin's disease. In children, deficiencies in the cell-mediated immunity system greatly increase the risk of lymphomas, including Hodgkin's disease.

References: [18, 25, 31, 47, 49, 51, 53, 54, 72, 101, 112, 123, 124, 140, 141, 174-176, 188]

SECTION



3

factors associated with high or low risks of cancer

SECTION 3

Factors Associated with High or Low Risks of Cancer

28. Does cancer run in families?

Familial aggregations of cancer have long attracted attention. Nearly everyone knows at least one person who has had several close relatives with cancer. However, cancer is a common disease and some such "clustering" of cases would be expected on the basis of chance alone. In studying this problem, the appropriate question is whether such clustering exceeds that to be expected on the basis of a random distribution of cases throughout the population and, if this is so, what is the magnitude of the excess risk among relatives of cancer patients?

Virtually every form of cancer which has been studied in the laboratory has shown an increased frequency in some species and strain of animals. It would be surprising if the same were not true for cancer in man. The results of animal work on strain differences in the risk of cancer suggest that human studies should consider familial patterns of risk for specific forms of cancer, as well as all forms combined.

The limited data available do suggest some increased familial risk of developing cancer of the same site for cancers of the female breast, stomach, large intestine, endometrium, prostate, lung, and possibly ovary. However, it is not known to what extent the observed familial aggregation of these tumors is due to genetic characteristics or to enviromental factors, such as diet or occupation, which may remain the same from one generation to the next. Several "cancer family syndromes" have also been described in which family members present excess numbers of specific combinations of tumors such as adenocarcinomas of the colon, stomach, and endometrium; sarcomas and breast cancers; breast and ovary car-

cinomas; and brain tumors and sarcomas. It is interesting to note that these site combinations are similar to those which occur as multiple primaries within the same individual at frequencies higher than expected.

Brain tumors and sarcomas seem to occur more frequently than expected in brothers and sisters of children with these tumors. When an identical twin has childhood leukemia, the probability that the other twin will develop the disease within 1-2 years of the date of diagnosis of the first twin is about 1 in 5, a magnitude of risk far exceeding the prevailing level in the general population. Retinoblastoma, a rare form of cancer of the eye, is known to be due to a mutation inherited as an autosomal dominant. The nevoid basal cell carcinoma syndrome and pheochromocytoma with medullary thyroid carcinoma show similar patterns. In addition, several precancerous conditions including familial polyposis of the colon, neurofibromatosis, xeroderma pigmentosum, and albinism show marked hereditary patterns.

Although familial aggregations have not been demonstrated, some associations are known to exist between chromosome structure and malignancy. Persons with mongolism (Down's syndrome) have an extra chromosome and also are at excess risk of acute leukemia. Many individuals with chronic myeloid (granulocytic) leukemia have part of one chromosome missing (Philadelphia chromosome). Some associations between blood type and certain forms of cancer have been reported, but no assessment of the meaning of these observations is possible at this time.

References: [70, 71, 122, 142]

29. Is a person who has already had one cancer likely to develop a second cancer?

The occurrence of multiple cancers in the same person (two or more primary malignant tumors in different locations) was first reported by Billroth about a century ago. Since then, there have been countless reports of such cases by various writers with differing definitions of the term "multiple". It is now generally agreed that cancer of certain sites is associated with a very substantial excess risk of a second cancer in the same organ (skin, oral cavity, and large intestine and rectum) or in a paired organ (opposite breast, opposite ovary, perhaps opposite lung), presumably due to the same factors responsible for the first primary.

Despite the apparent lack of any substantial increase in the overall incidence among cancer patients of new primary tumors in different organs, there is now good evidence that tumors of certain specific pairs of sites occur with increased or decreased frequency.

Site pairs which seem to occur with unusually high frequency include the following:

breast and uterine corpus (endometrium)
breast and ovary
endometrium and ovary
colon and endometrium
colon and breast
cervix and rectum
cervix and urinary bladder
rectum and bladder
different sites in the upper digestive and respiratory systems
salivary glands and breast
lip and intraoral sites, skin

The number of individuals actually developing second primary tumors is quite small compared to those developing first tumors, and definitive study of multiple cancers in man requires access to a very large volume of case material. Development of more large-scale cancer registries covering defined populations will permit the accumulation of more accurate and detailed data on the risk of developing two or more independent tumors.

References: [29, 153]

30. Is cancer mortality for married persons different from that for single persons?

In the United States and most other countries, married persons generally experience a lower risk than single persons in mortality from most causes of death, including cancer. The apparently lower mortality of married persons may be, in part, the result of errors in reporting marital status to census enumerators and on death certificates. Another factor may be self-selection in marriage, since persons in poor health are less likely to marry or remarry.

The contrast in cancer mortality by marital status is more marked among males than among females, particularly in tumors of the buccal cavity and pharynx (table 15). Among females, differences with respect to marital status are relatively small, with the exception of mortality from breast cancer and from cancer of the genital organs, primarily uterine cervix. The differences for breast and cervix are too large to arise from reporting and classification errors alone and it is generally accepted that they reflect the presence of real differences in risk.

Incidence data from several sources support the U.S. mortality data in showing higher cancer rates among single than among married persons, especially for female breast cancer. The difference in risk of developing cancer of the reproductive organs between mar-

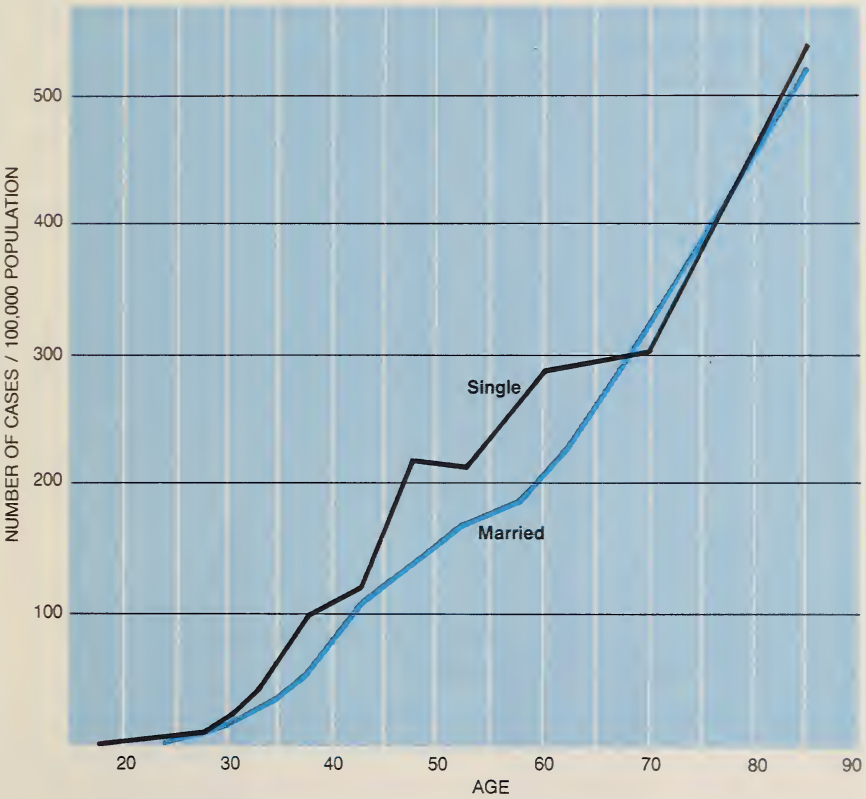
TABLE 15. RATIOS OF AGE-ADJUSTED CANCER DEATH RATES FOR PERSONS AGE 15 AND OVER OF SINGLE, WIDOWED AND DIVORCED TO MARRIED PERSONS, BY SELECTED SITES OR GROUPS OF SITES, COLOR, AND SEX: United States, 1959-61. (Adjusted to 1960 U. S. population.)

COLOR AND PRIMARY SITES	MALES			FEMALES		
	SINGLE TO MARRIED	WIDOWED TO MARRIED	DIVORCED TO MARRIED	SINGLE TO MARRIED	WIDOWED TO MARRIED	DIVORCED TO MARRIED
WHITE						
Buccal cavity and pharynx (140-148)	2.16	2.12	4.10	0.87	1.47	1.67
Digestive organs and peritoneum (150-159)	1.26	1.31	1.53	1.14	1.18	1.15
Respiratory system (160-165)	1.16	1.45	2.11	1.04	1.23	1.49
Breast (170)	2.50	2.50	2.50	1.41	1.02	1.13
Cervix uteri (171)	...	...	...	0.60	1.66	2.38
Female genital organs excluding cervix (172-176)	...	...	...	1.47	1.22	1.24
Prostate (177)	0.90	1.13	1.30	...	...	...
Male genital organs except prostate (178, 179)	1.50	0.64	1.79	...	...	...
All urinary organs (180, 181)	1.10	1.28	1.52	1.08	1.25	1.40
Other and unspecified sites (190-199)	1.26	1.33	1.70	1.17	1.29	1.22
Lymphatic and hematopoietic tissues (200-205)	0.98	0.96	1.21	1.08	1.10	1.05
NONWHITE						
Buccal cavity and pharynx (140-148)	2.08	2.64	3.14	1.50	1.94	1.44
Digestive organs and peritoneum (150-159)	1.35	1.76	1.78	1.21	1.57	1.42
Respiratory system (160-165)	1.51	1.74	2.46	1.23	1.63	1.89
Breast (170)	1.67	3.33	2.00	1.31	1.41	1.42
Cervix uteri (171)	...	...	...	1.17	1.84	1.60
Female genital organs excluding cervix (172-176)	...	...	...	1.44	1.54	1.45
Prostate (177)	0.88	1.52	1.45	...	...	...
Male genital organs except prostate (178, 179)	1.77	1.54	2.69	...	...	...
All urinary organs (180, 181)	1.17	2.16	1.83	1.13	1.68	1.70
Other and unspecified sites (190-199)	1.34	1.87	1.95	1.31	1.49	1.37
Lymphatic and hematopoietic tissues (200-205)	1.06	1.34	1.65	1.12	1.32	1.71

Source: [120]

ried and single females is concentrated within certain age groups, as illustrated by breast cancer in figure 21. The difference is most marked in the age range 30 to 65 years and is not a prominent characteristic at younger or older ages.

FIGURE 21. BREAST CANCER INCIDENCE RATES, BY MARITAL STATUS: White females in ten urban areas of the United States, 1947.



Source: [4]

Some studies have suggested an above-average incidence of breast cancer not only among single women but also among married women who have had no or few pregnancies. Pregnancy at an early age seems to confer a protective effect. (See also Question 24.) The complex relationships between marital status and cervical cancer have been noted in question 25. There is virtually no evidence of transmission of cancer between marital partners.

References: [120]

31. Does the occurrence of cancer vary with a person's social or economic status?

The present evidence on the distribution of cancer by socioeconomic class comes from the United States and some countries in Western Europe. These sources indicate persons in lower socioeconomic groups to have above-average incidence and mortality rates for cancer of all sites combined. Figure 22 shows that this association is more regular in the United States than in Denmark or in England and Wales, and may be somewhat stronger among males than among females.

The intensity and direction of the gradient between cancer and socioeconomic status vary with site of malignancy. Thus, table 16 shows the association with low socioeconomic status to be generally quite marked for cancer of the cervix, esophagus, and stomach, but smaller and in the opposite direction for cancer of the female breast. The lowest income group has the highest incidence for cancers of the buccal cavity and respiratory system.

The relationships between cancer risk and socioeconomic status are not fully understood, but differences in general way of life, quality of medical care, and degree of exposure to carcinogenic materials in the environment may be contributing factors. Under these circumstances later findings from cancer registries in developing countries may differ from those described here with respect to both the sites displaying socioeconomic class gradients and size of the gradients.

References: [46, 120]

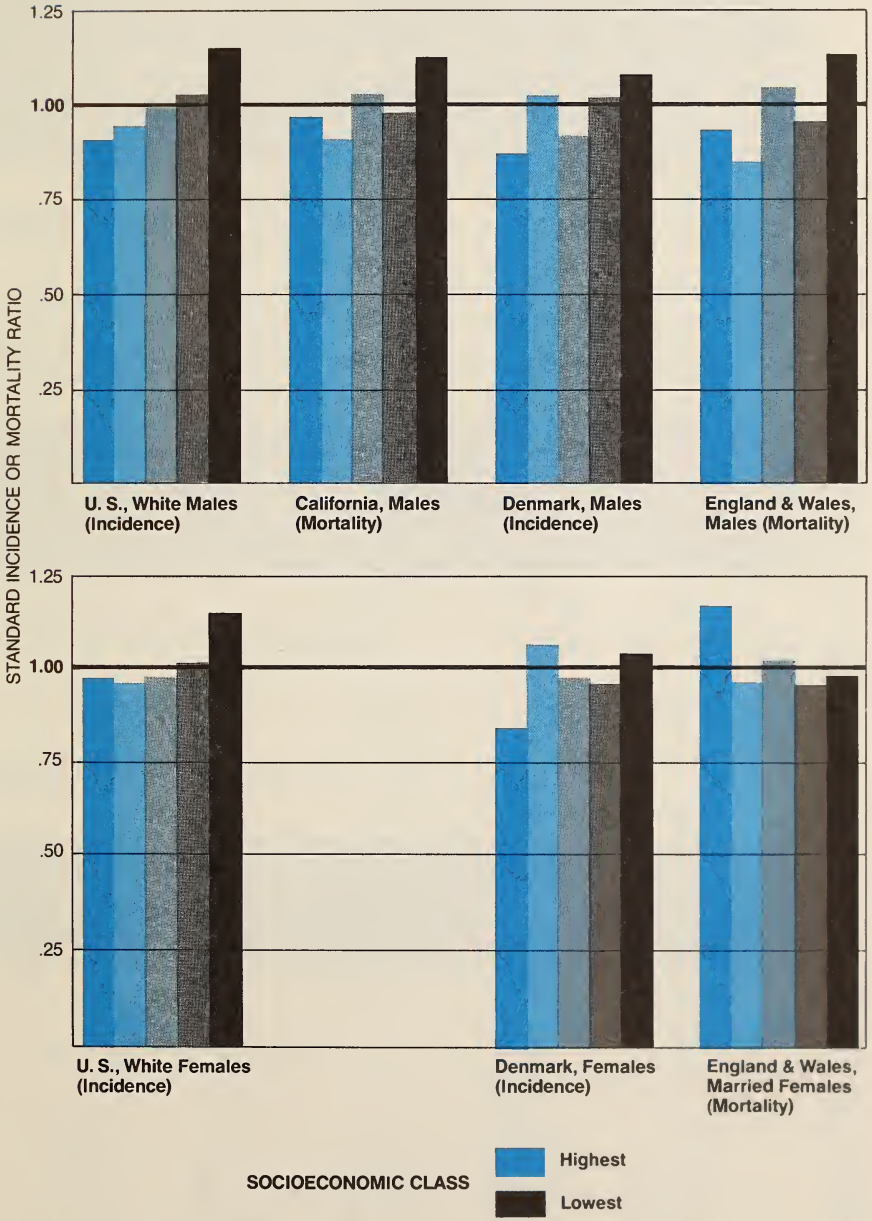
32. What cancers are associated with special social customs or living habits?

In contrast to occupational and industrial malignancies, which have been reported most often in Western populations, cancers related to special social customs or living habits have been noted as a rule in tropical and Oriental countries. However, this impression may be incorrect because customs and habits in Western populations do not show the extreme diversity found elsewhere, so that opportunities for identifying and contrasting the effects of widely different exposures are less frequently recognized.

Table 17 summarizes some of the known associations between cancer frequency and certain customs or habits. Cancer of the oral cavity has been linked with betel chewing in southeast Asia. In India a similar effect has been observed from the chewing of khaini, a mixture of tobacco and lime. Where cigars are smoked with the lighted end in the mouth, a Kashmiri custom called chutta, cancer of the hard palate sometimes results.

Keeping a heating pot next to the abdomen, a common practice in Kashmir and Japan, is often associated with skin cancer at that site. Cancers in the skin covered by a loin cloth (dhoti) are com-

FIGURE 22. INCIDENCE AND MORTALITY RATIOS FOR CANCER, BY SOCIOECONOMIC STATUS AND SEX.



Source: [1]

TABLE 16. STANDARDIZED INCIDENCE AND MORTALITY RATIOS FOR CANCER OF ALL SITES AND FOR SELECTED SITES, BY SOCIOECONOMIC CLASS AND SEX: United States, Denmark, and England and Wales.

SITE	CLASS	U. S. WHITE, 10 CITIES 1947 (INCIDENCE)		U. S. MALE IN CALIFORNIA, 20-64 YEARS OF AGE, 1949-51 (MORTALITY)	DENMARK, 1943-47 (INCIDENCE)		ENGLAND AND WALES, 20-64 YEARS OF AGE, 1949-53 (MORTALITY)		
		MALE	FEMALE		MALE	FEMALE	MALE*	FEMALE	
								MARRIED†	SINGLE*
All sites	I (Highest)	90	97	97	87	84	94	116	116
	II	94	96	90	102	105	86	97	95
	III	98	97	103	91	97	104	102	107
	IV	102	101	97	101	96	95	96	90
	V (Lowest)	115	114	112	107	104	113	98	89
Buccal cavity and pharynx	I			67					
	II			80					
	III			102					
	IV			112					
	V			100					
Esophagus	I	55	94	54	104		132	96	33
	II	88	100	67	103		92	99	96
	III	105	91	86	67		91	97	89
	IV	102	91	115	80		98	87	100
	V	137	138	145	122		130	126	46
Stomach	I	71	80	51	87	76	57	68	108
	II	90	98	72	89	101	70	80	77
	III	102	98	93	89	93	101	102	96
	IV	105	112	99	119	104	112	110	107
	V	124	112	165	108	107	130	119	132
Large intestine	I	101	99		101	100	121	115	125
	II	102	97		99	79	101	106	100
	III	102	97		88	87	102	99	111
	IV	94	105		116	115	92	101	87
	V	100	105		93	126	99	94	84

Rectum	I	92	100		85	70	86	107	114
	II	108	93		100	109	86	93	89
	III	99	99		106	93	108	104	109
	IV	97	103		103	100	94	105	94
	V	104	108		100	106	104	93	74
Lung and bronchus	I	67	98	85	66		81	119	75
	II	78	88	77	99		82	95	101
	III	99	98	112	90		107	102	112
	IV	118	99	108	97		91	98	100
	V	134	126	112	116		118	96	91
Breast	I		107			93	80	137	116
	II		103			112	118	110	105
	III		97			110	101	104	113
	IV		99			94	119	84	83
	V		98			92	68	85	84
Prostate	I	88		135	78		128		
	II	106		112	106		99		
	III	96		96	71		102		
	IV	98		88	107		93		
	V	112		107	114		102		
Cervix uteri	I		74			50		64	40
	II		85			90		75	61
	III		90			79		98	87
	IV		113			100		105	121
	V		156			131		134	115
Corpus uteri	I		105			87		103	180
	II		101			90		93	93
	III		100			109		106	125
	IV		87			108		92	59
	V		110			101		99	61

Source: [1] *All occupied and retired persons. †Classified by husband's occupation.

TABLE 17. SOCIAL CUSTOMS AND LIVING HABITS* ASSOCIATED WITH CANCER OF SELECTED SITES.

AGENT	ORGANS AFFECTED	GEOGRAPHIC DISTRIBUTION
Tobacco products:		
Betel quid (areca nut, tobacco, lime, buyo leaf).	Oral cavity, cheek, lip	India, Indo China, Philippines, Siam, Formosa, Ceylon, Malaysia.
Khaini quid (tobacco, lime)	Lip, gum	India.
Tobacco quid	Oral cavity	Europe, America.
Tobacco smoke	Lip, oral cavity, larynx, lung.	Worldwide.
Chutta (inverted smoking of cigars, smoke plus burns).	Oral cavity, tongue, palate.	Kashmir, Central America.
Thermic burns:		
Kangri (heating vessel)	Skin, abdominal	Kashmir.
Kairo (heating vessel)	Skin, abdominal	Japan.
Kang (heated brick platform)	Skin, hip	China.
Customs:		
Dhoti (loin cloth)	Skin (groin, abdomen)	India.
Noncircumcision	Penis	China.

*Excludes cancers related to diet or alcohol, for which see question 35; tobacco smoking is discussed in more detail in questions 33 and 34.
Source: [1]

monplace in India. Circumcision, on the other hand, almost completely prevents cancer of the penis if done soon after birth, and greatly reduces incidence rates even when done later in life.

References: [1, 154]

33. Is cigarette smoking related to lung cancer?

Yes. During the past 25 years a strong association between smoking of cigarettes and lung cancer has been reported by many investigators. No one now seriously disputes that lung cancer deaths occur much more frequently among cigarette smokers than among nonsmokers, and recent research has been directed toward elucidating the meaning of this correlation.

Because of the importance of the relation between smoking and various medical conditions, the U.S. Public Health Service in 1962 appointed an expert committee to assess the nature and magnitude of the health hazard. The report of this committee was the most extensive and most detailed review of the problem up to that time and is recommended reading for anyone seeking information on the subject. Since then, the Public Health Service has published several

reports updating and expanding the evidence. The most recent reports for 1971 and 1972 concluded as follows:

a. Epidemiological evidence derived from a number of prospective (table 18) and retrospective studies in the United States, Canada, Europe, and Japan coupled with experimental and pathological evidence confirms the conclusion that cigarette smoking is the main cause of lung cancer in men. These studies reveal that the risk of developing lung cancer increases with the number of cigarettes smoked per day, the duration of smoking, and earlier initiation, and diminishes with cessation of smoking.

b. Cigarette smoking is a cause of lung cancer in women but accounts for a smaller proportion of cases than in men. The mortality rates for women who smoke, although significantly higher than for female nonsmokers, are lower than for men who smoke. This difference may be at least partially attributed to difference in exposure: the use of fewer cigarettes per day, the use of filtered and low "tar" cigarettes, and lower levels of inhalation. Nevertheless, even when women are compared with men who apparently have similar levels of exposure to cigarette smoke, the mortality ratios appear to be lower in women.

c. The risk of developing lung cancer among pipe and/or cigar smokers is higher than for nonsmokers but significantly lower than for cigarette smokers.

d. The risk of developing lung cancer appears to be higher among smokers who smoke high "tar" cigarettes or smoke in such a manner as to produce higher levels of "tar" in the inhaled smoke.

e. Ex-cigarette smokers have significantly lower death rates for lung cancer than continuing smokers. The decline in risk following cessation appears to be rapid both for those who have smoked for long periods of time and for those with a shorter smoking history, with the sharpest reductions taking place after the first two years of cessation. There is evidence to support the view that cessation of smoking by large numbers of cigarette smokers would be followed by lower lung cancer death rates.

f. The risk of developing lung cancer appears to be higher for smokers who have chronic bronchitis. Though both conditions are directly related to the amount and duration of smoking, an additional risk for lung cancer appears to exist for cigarette smokers with chronic bronchitis which is independent of age and number of cigarettes consumed.

g. Increased death rates from lung cancer have been observed among urban populations when compared with populations from rural environments. The evidence concerning the role of air pollution in the etiology of lung cancer is presently inconclusive. Factors such as occupational and smoking habit differences may also con-

TABLE 18. LUNG CANCER MORTALITY RATIOS REPORTED BY 8 PROSPECTIVE STUDIES.

AUTHOR, YEAR, COUNTRY, REFERENCE	NUMBER AND TYPE OF POPULATION	FOLLOW-UP (YEARS)	SMOKING CATEGORY	NUMBER OF DEATHS*	MORTALITY RATIO
Hammond and Horn, 1958, USA, Ref: [88]	187,783 white males in 9 states, ages 50-69	3½	Non-smokers	15	1.0
			Cigarette Smokers		
			Total	397†	10.7
			Less than 10 cigs/day	24	8.0
			10-20 cigs/day	84	10.5
			More than 20 cigs/day	117	23.4
			Pipe smokers	18	2.6
			Cigar smokers	7	1.0
Doll and Hill, 1964, Great Britain, Ref: [59]	Approximately 41,000 male British physicians	10	Non-smokers	3	1.0
			Cigarette smokers		
			1-14 cigs/day	22	8.1
			15-24 cigs/day	53	19.9
			25 or more cigs/day	57	32.4
			Pipe & cigar smokers		
			1-14 grams/day	12	6.0
			15-24 grams/day	6	6.4
			25 or more grams/day	3	13.7
Best, 1966, Canada, Ref: [30]	Approximately 78,000 male Canadian veterans	6	Non-smokers	7	1.0
			Cigarette smokers		
			Total	245	14.2
			Less than 10 cigs/day	57	10.0
			10-20 cigs/day	204	16.4
			More than 20 cigs/day	63	17.3
			Pipe smokers	18	4.4
			Cigar smokers	2	2.9
Kahn (Dorn), 1966, USA, Ref: [107]	Approximately 293,000 U. S. male veterans	8½	Non-smokers	78	1.0
			Cigarette smokers		
			Total	749	12.1
			1-9 cigs/day	45	5.5
			10-20 cigs/day	303	9.9
			21-39 cigs/day	315	17.4
			More than 39 cigs/day	82	23.9
			Pipe smokers	17	1.8
			Cigar smokers	6	1.6
			Pipe & cigar smokers	20	1.7

Hammond, 1966, USA, Ref: [87]	440,558 males 562,671 females 35-84 years old in 25 states	4	Males: Non-smokers Current cig. smokers Total 1-9 cigs/day 10-19 cigs/day 20-39 cigs/day 40 or more cigs/day Pipe smokers Cigar smokers Pipe & cigar smokers Females: Non-smokers Current cig. smokers Total 1-19 cigs/day 20 or more cigs/day	 49 719 26 82 381 82 21 22 11 102 81 20 50	 1.0 9.2 4.6 7.5 13.1 16.6 2.2 1.8 0.9 1.0 2.2 1.1 4.8
Buell et al., 1967, USA, Ref: [34]	69,868 American Legionnaires	3	Non-smokers Cigarette smokers Less than 20 cigs/day 20 cigs/day More than 20 cigs/day	NR NR NR NR	1.0 2.3 3.5 4.9
Hirayama, 1967, Japan, Ref: [99]	265,118 male and female adults 40 years of age and over	1½	Non-smokers Cigarette smokers 1-24 cigs/day 25 or more cigs/day	3 29 5	1.0 2.7 5.7
Weir and Dunn, 1970, USA, Ref: [178]	68,153 males in various occupations in California	5-8	Non-smokers Cigarette smokers Total Approx. 10 cigs/day Approx. 20 cigs/day 30 or more cigs/day	NR NR NR NR NR	1.0 7.6 3.7 9.0 9.6

NR—Not Reported.

*Unless otherwise specified, disparities between the total number of deaths and the sum of the individual smoking categories are due to the exclusion of occasional, miscellaneous, mixed, or exsmokers.

†Includes cases not microscopically confirmed, whereas other numbers from this study include only those microscopically confirmed.

tribute to the urban-rural difference observed. Detailed epidemiologic surveys have shown that the urban factor exerts a small influence compared to the overriding effect of cigarette smoking in the development of lung cancer.

h. Certain occupational exposures have been found to be associated with an increased risk of dying from lung cancer. Cigarette smoking interacts with these exposures in the pathogenesis of lung cancer so as to produce very much higher lung cancer death rates in those cigarette smokers who are also exposed to such substances.

i. Experimental studies on animals utilizing skin painting, tracheal instillation or implantation, and inhalation of cigarette smoke or its component compounds have confirmed the presence of complete carcinogens as well as tumor initiators and promoters in tobacco smoke. Recently, other compounds have been described that have no independent activity in two-stage carcinogenesis but accelerate the carcinogenic effects of polynuclear aromatic hydrocarbons in initiator-promoter systems.

References: [30, 34, 59, 87, 88, 99, 107, 161, 168, 169, 178]

34. Is smoking related to cancers of other sites?

The Public Health Service has also reported the following relationships between cigarette smoking and cancers of other sites:

Cancer of the Larynx

a. Epidemiological, experimental, and pathological studies support the conclusion that cigarette smoking is a significant factor in the causation of cancer of the larynx.

b. The risk of developing laryngeal cancer among cigarette smokers as well as pipe and/or cigar smokers is significantly higher than among nonsmokers.

c. The magnitude of the risk for pipe and cigar smokers is about the same order as that for cigarette smokers.

d. Experimental exposure to the passive inhalation of cigarette smoke has been observed to produce premalignant and malignant changes in the larynx of hamsters.

Cancer of the Oral Cavity

a. Epidemiological and experimental studies contribute to the conclusion that smoking is a significant factor in the development of cancer of the oral cavity and that pipe smoking, alone or in conjunction with other forms of tobacco use, is causally related to cancer of the lip.

b. Experimental studies suggest that tobacco extracts and tobacco smoke contain initiators and promoters of cancerous changes in the oral cavity.

Cancer of the Esophagus

a. Epidemiological studies have demonstrated that cigarette smoking is associated with the development of cancer of the esophagus.

b. The risk of developing esophageal cancer among pipe and/or cigar smokers is greater than that for nonsmokers and of about the same order of magnitude as for cigarette smokers, or perhaps slightly lower.

c. Epidemiological studies have also indicated an association between esophageal cancer and alcohol consumption. The combined exposure of alcohol consumption and cigarette smoking is associated with especially high rates of cancer of the esophagus.

Cancer of the Urinary Bladder

a. Epidemiological studies have demonstrated a significant association between cigarette smoking and cancer of the urinary bladder in both men and women. These studies demonstrate that the risk of developing bladder cancer increases with inhalation and the number of cigarettes smoked.

b. Clinical and pathological studies have suggested that tobacco smoking may be related to alterations in the metabolism of tryptophan and may in this way contribute to the development of urinary tract cancer.

Although many questions about the carcinogenic effects of tobacco remain to be answered, and other factors may be implicated as additional data accumulate, it is now clear that cigarette smoking has been implicated as an important factor in the production of cancer of the lung and several other sites, and that a significant reduction in the use of cigarettes would be followed by a substantial decrease in mortality from these diseases.

References: [168, 169]

35. What is known about diet and alcohol in relation to cancer incidence?

Many different organic chemicals have been used to induce cancer in laboratory animals; some of these occur in small amounts in ordinary food products. Some synthetic dyes or flavors formerly used in food preparation have produced cancers in experimental animals. Animal experiments also suggest that there may be some risk of cancer associated with the increasing use of natural and synthetic estrogen preparations in medicine and cosmetics and in the fattening and tenderizing of animals prior to slaughter and consumption. Other potentially hazardous agents are known to be formed or introduced in small quantities during food preparation and cooking. The irritation caused by frequent consumption of alcohol or certain con-

diments constitutes another possible source of risk. In addition to such direct effects, diet may play a role in raising or lowering tissue susceptibility to cancer-producing materials (cocarcinogenesis); for example, obese animals have an increased incidence of some forms of cancer when compared with lean animals of the same species kept under identical conditions except for limitation of food intake. Experiments with germ-free rats showing that cycasin, which is naturally present in cycad nuts, is metabolized to its aglycone, a carcinogen, by an enzyme of bacterial origin illustrate a link between diet and cancer.

In contrast to the many and varied possibilities suggested by animal work, observations on human populations have so far uncovered relatively few forms of cancer that can be linked with diet. The high incidence of cancer of the oropharynx and esophagus among residents of the far north of Sweden and Finland is probably related to multiple dietary deficiencies which result in a high frequency of atrophic changes in the mucosa (Plummer-Vinson syndrome); these changes may in turn be precursors of cancer. Iodine deficiency may be related to development of cancer of the thyroid. Undernourishment or malnourishment may contribute to the high frequency of cirrhosis of the liver and the later appearance of liver cancer among some groups of African Negroes, Chinese, Japanese, and others; aflatoxin, a liver carcinogen, has been identified as a contaminant of nuts and other foodstuffs in areas of high liver cancer incidence.

The association between excessive alcohol consumption and cancer of the buccal cavity, pharynx, larynx, and esophagus is now well established. Persons drinking large quantities of alcohol may well have nutritional deficiencies leaving them more susceptible to the action of the alcohol, tobacco, or other agents. Carcinogenic contamination has also been suggested as a possible by-product of fermentation and distillation of some wines and brandies.

An excess risk among obese women has been shown for cancers of the endometrium, pancreas, gallbladder, and breast; the interaction of hormonal factors and diet is not clear at this time. The role, if any, of trace elements in the diet has not been ascertained either for all cancers or cancers of specific sites.

Detection of associations between commonly used foods and cancer is difficult in populations where nearly everyone adheres to the same basic diet, so that hypotheses on dietary effects have been generated by comparisons of the disease experience of populations living under widely different conditions. It is evidence from the latter source, for example, that has given rise to speculation linking the highly refined Western diet, rich in starches and deficient in bulk, with the elevated risks for bowel cancer in North America and Western Europe.

The shifts in site-specific cancer experience among migrant populations support inferences on the presence of large intercountry differences in cancer risk. Furthermore, the natural experiment represented by the variable rates of adaptation by migrants to their new environment offers opportunities to reopen the question of diet and cancer. Cancers of the stomach and large bowel among the Japanese in Hawaii are being studied from this point of view, and associations of foods preserved or pickled in salt with stomach cancer and of beef with large bowel cancer have been reported. While such findings are not conclusive and require confirmation, they do represent leads useful for the planning of future research on diet and cancer.

References: [40, 78, 81, 85, 86, 116, 171, 186]

36. Is radiation a significant cause of cancer?

There is clear evidence that radiation can cause cancer in human beings. Although at present the number of tumors induced by artificial radiation constitutes only a very tiny fraction of all human cancer, the hazard will probably increase in the years to come. While natural background radiation has been present for ages, the increasing importance of radiation as a health problem for man arises from two modifications of his environment: increasing use of radioactive substances in industry and medicine, and tests of nuclear weapons and the consequent fallout. Most of the demonstrable radiation hazard in the United States comes from industrial and medical uses of X-rays and radioactive isotopes.

Radiation may produce many different types of malignancy depending on the nature of the exposure. The early radium workers developed skin cancers and leukemias; later, osteogenic sarcomas developed in radium-dial painters. Radiologists who were exposed before the dangers were known and protective measures taken have been shown to have an excess mortality from leukemia. Uranium mine workers have developed lung cancer at higher rates than the general population. The survivors of the atomic bombs in Hiroshima and Nagasaki have experienced excessive morbidity and mortality from acute leukemia, especially in the first ten years following the war; elevated risks of other malignant neoplasms among the survivors have become increasingly evident since 1950.

Patients treated with radiotherapy for other conditions have also experienced increased cancer risks. There is convincing evidence that radiation of the neck in infants, once a common treatment for enlargement of the thymus, is associated with an increased incidence of thyroid cancer. Irradiation of the spine for ankylosing spondylitis resulted in an excess of leukemia and lung cancers. There is some evidence that exposure of pregnant women to diag-

nostic X-rays is associated with subsequent development of leukemia and other malignancies in their children.

The collective information on dose-response relationship from the several studies, especially those carried out on the atomic bomb survivors, is compatible with a theoretical model based on a linear relationship; threshold limits below which there is no effect have not been established with certainty. Further investigations are needed to measure with more precision the frequency of radiation-induced malignancies and to determine the relation between radiation dose, latent period, and cancer incidence rates.

References: [23, 102, 131, 177]

37. What is known about the occurrence of cancer among people in different occupations?

An association between occupation and the occurrence of cancer was recognized before the advent of the modern industrial era. The classic example is the high risk of scrotal cancer among English chimney sweeps, first reported by Percivall Potts in 1775. The immense growth of modern industry has brought with it an increasing number and diversity of carcinogenic substances, many of which are associated with particular occupations or industries. Some of the known occupational cancers are listed in table 19.

A different approach to the study of cancer and occupation is afforded by mortality statistics of broad occupational groups. Such statistics for the United States are summarized in table 20. More detailed tables show that miners, laborers, and transportation workers have an increased risk of cancer, while men in agricultural pursuits (nearly all of whom live in rural areas) have comparatively low mortality rates for all cancer sites except skin. These findings are confirmed by similar data collected in England and Wales.

The combination of a long latent period between exposure and the development of cancer, changes in exposure with time, incomplete diagnosis of some types of tumor, errors in reporting occupation in censuses and on death certificates, effects attributable to nonoccupational agents, and other factors make it difficult to detect small increases (twofold or less) in cancer risk in specific occupation groups.

References: [91]

38. Is the incidence of cancer related to air pollution?

It is helpful to distinguish two kinds of air pollution: general pollution of the outdoor air (by such substances as industrial smoke and fumes, automobile exhaust, or products of combustion from home heating) and pollution of the air in a certain limited area (such as a

TABLE 19. CARCINOGENIC AGENTS WHICH MAY BE ASSOCIATED WITH VARIOUS OCCUPATIONS.

AGENT	SITES OF CANCER	AREAS WHERE NOTED
SPECIFIC AGENTS:		
Arsenic	Skin, lung	United States, Great Britain, Germany, France, Argentina, Taiwan, African countries
Coal tar, pitch	Skin, lung	United States, Great Britain
Petroleum	Skin, lung	United States, France, Great Britain, Austria
Shale oils	Skin	United States, Great Britain
Lignite tar & paraffin	Skin	Great Britain, France
Creosote oils	Skin	United States, Great Britain
Anthracene oils	Skin	Great Britain
Soot carbon black	Skin	United States, Great Britain
Mustard gas	Lung	Japan
Cutting (mineral) oils	Skin, poss. respiratory & upper alimentary tract	Great Britain, Australia
Products of coal carbonization	Lung, bladder	Great Britain, United States, Japan
Sunlight	Skin	United States, Argentina, Australia, France, et al.
Chromates	Lung	United States, Great Britain, Germany, Canada
Asbestos	Lung, pleura, peritoneum, GI tract	United States, Great Britain, Germany, Canada, S. Africa, Holland, Australia, USSR, Italy, et al.
Aromatic amines, dyes, rubber	Bladder, poss. biliary tract, salivary glands	United States, Germany, Great Britain, Switzerland, et al.
X-rays and radium	Skin, lung, leukemia	United States and many other areas
Nickel	Lung, nasal cavity & sinus	Great Britain, Norway, Canada
Benzol	Leukemia	United States, et al.
Isopropyl oil	Lung, larynx, nasal sinus	United States
Radioactive chemicals	Bones, nasal sinus	United States
Chemicals (various)	Lymphoma, pancreas	United States
NON-SPECIFIC (OCCUPATIONS):		
Wood Furniture working	Nasal cavity, sinuses	Great Britain, United States
Leather working	Nasal cavity, sinuses, bladder	Great Britain, United States
Soft Coal mining	Stomach	United States (1 report)

Source: [1]

TABLE 20. STANDARDIZED MORTALITY RATIOS FOR ALL SITES OF CANCER COMBINED, AND FOR CANCER OF SELECTED SITES, BY BROAD OCCUPATIONAL GROUP, WHITE MALE POPULATION OF UNITED STATES AGED 20-64, 1950.

BROAD OCCUPATIONAL GROUP	ALL SITES	BUCCAL CAVITY AND PHARYNX	ESOPHAGUS	STOMACH	LARGE INTESTINE	RECTUM	LUNG AND BRONCHUS	BLADDER	SKIN	LEUKEMIA AND ALEUKEMIA
All persons aged 20-64	100	100	100	100	100	100	100	100	100	100
Professional, technical, and kindred workers	91	83	68	64	124	111	82	97	93	114
Farmers and farm managers	81	62	35	91	81	64	55	73	133	127
Managers, officials, and proprietors, except farm	95	83	64	74	110	94	95	85	105	111
Clerical and kindred workers	92	100	77	69	118	103	94	115	93	93
Salesworkers	102	93	70	75	114	113	103	111	137	106
Craftsmen, foremen, and kindred workers	111	107	117	108	104	118	132	125	132	105
Operatives and kindred workers	101	105	122	102	105	111	110	99	128	92
Service workers, except private household	109	141	149	102	106	119	125	123	N.A.	91
Laborers, including farm laborers and foremen	105	133	166	116	95	94	103	96	213	96
Farm laborers and foremen	59	64	85	79	53	32	53	76	N.A.	72
Laborers, except farm and mine	123	161	182	130	108	113	123	104	172	106

N.A.=Not available.

Source: [1]

mine or an industrial plant) by specific substances. Occupational cancers were discussed in the previous question; however, only a small proportion of the population are directly exposed and these exposures can often be controlled or eliminated when the hazard is recognized.

General pollution of the air we breathe is found in all large cities and in many suburban and rural areas. The association between the incidence of cancer and the concentration of population and industry in urban areas has already been mentioned (question 13). Many aspects of urban living are different from that in the rural areas, and it is difficult to distinguish the separate effects. In addition, air pollution may be due to a number of substances, the quantities and proportions of which are variable from area to area and over time; some of the commonly used indices of air pollution are measures of suspended particulates, sulfates, nitrogen oxides, carbon monoxide, and hydrocarbons. Several attempts have been made to correlate the mortality and morbidity experience in metropolitan areas with indices of air pollution. One difficulty with this approach is that the latent period for many cancers is twenty to forty years, so that cases now being diagnosed may reflect exposures to an earlier environment. Also, the strong associations of chronic non-specific lung disease (CNSLD) and lung cancer with cigarette smoking tend to obscure the presence of air pollution effects. The collective findings from the studies undertaken have more strongly associated air pollution with CNSLD than with lung cancer, which seems to be only weakly linked. Associations of suspended air particulates with stomach cancer and cancer of the prostate have been described. Further investigations to define and measure the effects of air pollution on the incidence of cancer, and other diseases as well, are urgently needed.

References: [75, 79]

39. How is cancer associated with other diseases or conditions?

The incidence of several forms of cancer is clearly related to occurrence of other morbid conditions in the same tissues or organs. For example, an association between cirrhosis and primary liver cell carcinoma has been confirmed in several underdeveloped countries, with both probably being due to some third factor such as parasitic disease or the presence of environmental carcinogens. A "third-factor" postulate is needed to account for the absence of an association in the United States and Western Europe, where most cirrhosis is due to ingestion of alcohol and liver cancer is relatively rare. A positive association between cancer of the pancreas and diabetes

has been described, although the mechanism underlying this relationship is not clear.

Plummer-Vinson syndrome, an atrophic disease of the mucous membranes, is sometimes a precursor of carcinoma of the esophagus. Chronic infections, such as osteomyelitis, may sometimes lead to cancer, but it is generally agreed that acute infections do not. The role of injury, such as bruising or cutting, in producing cancer is not entirely settled, but most observers now agree that a single acute injury will not produce cancer. Chronic or repeated injuries to the same tissues have not been adequately studied to permit unqualified conclusions, but it seems probable that these also do not produce cancer under ordinary circumstances.

TABLE 21. CANCERS ASSOCIATED WITH CERTAIN CONGENITAL DEFECTS.

CONGENITAL DEFECT	CANCER
Down's, Bloom's, Fanconi's syndromes	leukemia
certain phakomatoses	glioma, medulloblastoma
congenital hemihypertrophy	Wilm's tumor, primary liver cancer, and adrenocortical neoplasia
aniridia	Wilm's tumor
dysgenic gonads	gonadoblastoma
immunologic disorders (ataxia, telangiectasia, Wiscott-Aldrich syndrome, agammaglobulinemia, Chediak-Higashi syndrome)	lymphoma

Source: [71]

Although cancer can cause very great mental distress, there is no acceptable evidence that mental distress or illness ever causes cancer. The appearance of cancer soon after severe mental or emotional strain has often been reported but seems to be entirely fortuitous.

Unusually low incidence rates of cancer have been reported for persons with tuberculosis, atherosclerosis, essential hypertension, and several other diseases; this has led to the contention that some antagonism or mutual inhibition exists between these conditions and cancer. However, careful statistical investigation has indicated that these apparent relationships are due to the fact that persons with

hypertension or other potentially fatal diseases are unlikely to live long enough to develop cancer. There is no acceptable evidence for the inhibition of malignancy by these diseases.

The study of possible associations between cancer and other intercurrent diseases requires control of numerous other factors known to be related to cancer risks. The problems are further compounded by difficulties in making a prompt and accurate diagnosis of one or both conditions and in distinguishing between the effects of cancer and of a primary independent disease.

Many questions of interpretation and inference from data on intercurrent diseases do not arise in the study of congenital defects. Table 21 lists some congenital defects for which there is clear evidence of associated increased risks of certain cancers.

The last entry is interesting in that not only has an increased risk of malignancy been observed with primary immunodeficiencies, but patients receiving immunosuppression therapy (for organ transplantation) also develop cancers at rates higher than expected. The identification of some tumor-specific antigens further supports the hypothesis that disorders of the immune defense system are involved in the etiology of some tumors.

References: [70, 73, 94, 108, 117, 132, 147]

40. Do benign diseases ever become malignant?

Any unusual proliferation of cells can be called a "new growth" or "neoplasm". Most of these are local growths with no serious consequences and are therefore called "benign". Although several forms of benign diseases are associated with a high cancer incidence rate, this does not necessarily imply a change from benign to malignant. Some of the benign diseases most often associated with cancer are leukoplakia of various sites, carcinoma-in-situ, osteitis deformans, and benign polyps.

Although leukoplakia is very common, there is no universal agreement on the exact definition of the word. Clinically, leukoplakia is any disorder of mucous membranes characterized by the presence of white patches or plaques. Most pathologists restrict the term to those lesions of mucous membranes which exhibit characteristic microscopic changes called epithelial atypia. This disagreement between clinical and pathological definitions contributes to the uncertainty and confusion of opinions regarding the malignant potential of leukoplakia.

Leukoplakia of the oral cavity probably does become malignant, although estimates of the frequency of malignant transformations vary from 2.5 to 100 percent. A stepwise transformation from normal tissue to leukoplakia to malignancy has been postulated in relation to many factors—local irritation, vitamin deficiency, poor oral hy-

giene, use of tobacco and alcohol, endocrine disturbances, and others. Multiple patches of leukoplakia are common; this might explain the high frequency of multiple malignant tumors within the oral cavity.

Leukoplakia of the urinary bladder can precede or accompany bladder cancer, but is most often found alone and is not widely accepted as a precancerous condition. Leukoplakia also occurs in the mucous membrane of many other organs, including pharynx, esophagus, cervix, vulva, conjunctiva, and penis. There is no general agreement on the malignant potential of leukoplakia in these areas.

Carcinoma-in-situ, sometimes called intraepithelial cancer, is a benign asymptomatic neoplastic condition characterized by a microscopic appearance of individual cells suggesting cancer, but without invasion of adjacent structures or metastases to distant lymph nodes or organs. It is most common in the uterine cervix, but is often seen in the oral cavity and elsewhere. Carcinoma-in-situ of the cervix has probably been studied more than any other benign neoplasm, but here too there is still disagreement concerning the nature of the events which may connect it with invasive cervical carcinoma.

Osteitis deformans, sometimes called Paget's disease of bone, seems to be related to several forms of bone cancer. Although osteosarcomas predominate, chondrosarcomas, fibrosarcomas, and other types of bone cancer have also been found in association with osteitis deformans. When cancer develops in an area of osteitis deformans, it is usually in an area where the disease is most advanced and has been present for many years. Such tumors are highly malignant and survival is usually short. A number of cases of multiple bone cancers arising in separate areas have been reported in Paget's disease.

Benign polyps are extremely common—in fact, very few persons are entirely free of them. They may occur almost anywhere in the skin, digestive tract, reproductive organs, respiratory system, or elsewhere. Study of the possible malignant transformation of benign polyps is greatly complicated by the fact that in its early stages cancer often has the gross appearance of a benign polyp. The only way to be sure that a polyp is completely benign is to examine it in its entirety under the microscope. This of course means that it can no longer give evidence of any malignant potential. However, some indirect information is available from careful statistical, clinical, and pathological studies. Thus, benign polyps of the nose and uterine cervix are generally agreed to have no relation to cancer of the same organs. Polyps of the endometrium are often associated with carcinoma, which may even be entirely confined to the polyp. However, it is never possible to say that the polyp was cancer free at an earlier stage, and for many endometrial polypoid lesions it may be unwise

to make a sharp distinction between benign and malignant. Polyps of the stomach are infrequent and it is not now possible to say whether they give rise to cancer. However, stomach carcinoma is more common among patients with multiple gastric polyps than among those with single polyps. Pernicious anemia has been reported to precede an increased incidence of both gastric polyps and carcinoma.

At present there is an active controversy about the significance of polyps in the large intestine and rectum. It is generally agreed that the uncommon villous papillomas are premalignant, and that the polyps found in familial polyposis or in ulcerative colitis at least indicate a high susceptibility to malignant disease in the lower digestive tract, whether or not the polyps themselves become cancer. However, the significance of benign adenomatous polyps, which are found in the colon or rectum of over 20 percent of the adult population, is not conclusively known despite extensive study of the subject.

References: [50, 82, 83]

41. Do viruses cause cancer?

The origin of a wide range of animal tumors has been linked to infection by viruses. Chicken sarcomas and leukemias were the first tumors discovered to be caused by RNA tumor viruses. Since then, many types of tumors occurring in mice, cats, hamsters, monkeys, and other animals have also been shown to be associated with RNA viruses. Several animal tumors are caused by DNA tumor viruses such as the polyoma virus and SV-40. Herpesviruses, which are DNA viruses, are responsible for yet other tumors in frogs, chickens, monkeys, and rabbits. The outcome of infection by a particular virus depends on species, strain, and age differences in susceptibility of the host animal, and on hormonal status, route of infection, and specific immunologic factors. The presence of certain combinations of factors may be required to elicit tumors.

To date there has been no demonstration of viral etiologies for human cancers that meet the exacting standards of proof for experimental work. Since the viral genome may actively be incorporated into the host DNA and the latent period may be very long, an essential element in the chain of proof—recovery of the virus—is extremely difficult to achieve. Studies attempting to find evidence for viral causation of leukemia, breast cancer, sarcomas, and other tumors in man have so far yielded conflicting or equivocal findings.

An etiologic role for the Epstein-Barr virus, a type of herpesvirus, in Burkitt's lymphoma is judged probable by several investigators (EB virus has also been implicated in nasopharyngeal cancer). Burkitt's lymphoma may represent an unusual and infrequent response to a common infection, since EB virus is strongly associated

with infectious mononucleosis. Cancer of the cervix, which recent work has linked to another herpesvirus, HSV-2, is another site currently being studied for possible viral etiology.

It has been suggested that tumor induction may require the triggering of latent viruses in the cell by an external physical or chemical agent. With the development and refinement of new laboratory techniques, one may anticipate in the coming years more detailed and convincing documentation of the case for viral etiologies of at least a few human tumors.

References: [20, 111, 149]

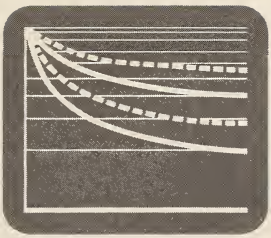
42. How is cancer in animals related to cancer in man?

Cancer is a general biological phenomenon. Although there are some differences in the appearance and behavior of cancer among various species, the abnormal growth and metastasis which characterize cancer can be found in all kinds of animals and cancerlike growths even occur in some plants. Neoplasms in invertebrate and lower vertebrate animals are the subject of intensive study. The epidemiology and etiology of tumors occurring among domestic animals are being investigated using information provided by animal tumor surveys and cancer registries maintained by schools of veterinary medicine. Transmission of cancer between animals has been shown for several species, including cats; this has led to concern about possible transmission between animals and man. However, no such transmission from pets to man has yet been demonstrated.

Many common forms of human cancer have close counterparts in laboratory animals. This fact has made possible much of the basic research in recent years which has had important implications in the study of the causation mechanism, and treatment of human cancer. The development of inbred strains of animals, especially mice, with distinct and well-characterized patterns of tumor incidence and growth has been especially valuable. However, man is not an inbred animal, nor do all animals respond in the same way to a given stimulus, so there will always be the problem of extrapolation of results from laboratory animals to man. Close liaison between experimentalists and epidemiologists is needed to devise new animal systems that will facilitate the extrapolation of animal findings to man.

References: [14, 60, 61, 89, 148, 160]

SECTION



4

treatment and survival of cancer patients

SECTION 4

Treatment and Survival of Cancer Patients

43. How may cancer be treated?

A patient with cancer may be treated by any one or a combination of several methods: surgical resection, radiation with X-rays or radioactive materials, chemicals or hormones, etc. The type of treatment used depends on many factors, such as site and microscopic appearance of the tumor, age and general health of the patient, stage of the tumor, knowledge and experience of the physician in charge of treatment, and facilities available.

Table 22 shows how cancer patients were generally treated in the United States in the period 1955-64 for the sites where tumors most frequently occur. The classification of therapy distinguishes surgical, radiological, hormonal and chemotherapeutic procedures. It is restricted to tumor-directed therapy and to the first course of treatment, which is defined to include all treatment initiated within a four month period after diagnosis. Surgical resection was the most used form of treatment. During the 10-year period, 55 percent of all patients were treated by surgical resection [*], 29 percent by radiation [*] and 18 percent by chemotherapy [*]. Although surgical resection has remained the treatment of choice, since the late 1960's more patients are receiving radiotherapy (34 percent) and chemotherapy (22 percent). Often a combination of two or more treatment methods may be more effective than any one method alone. In addition, a second or third course of treatment is frequently helpful if the primary treatment fails to cure or halt the growth of cancer.

References: [5]

[*] Alone or in combination with other therapy.

TABLE 22. PERCENT OF PATIENTS TREATED BY VARIOUS METHODS*, BY SITE, 1955-1964.

SITE	NUMBER OF CASES	SURGICAL RESECTION**	RADIATION**	SURGICAL RESECTION & RADIATION**	CHEMOTHERAPY/ HORMONES ONLY	NO DEFINITIVE Rx***
All Sites	219,485	45	19	10	8	19
Stomach	9,983	45	4	1	4	46
Colon	19,461	80	0	1	1	17
Rectum	11,515	75	2	1	1	21
Pancreas	5,374	7	6	0	7	80
Lung and Bronchus	22,585	21	35	5	9	29
Female Breast	25,698	62	5	25	3	4
Cervix uteri	10,557	14	71	8	0	6
Corpus uteri	7,614	39	20	35	1	5
Ovary	5,240	32	15	35	5	13
Prostate	13,790	57	3	4	28	8
Bladder	10,177	73	6	12	1	8
Hodgkin's disease	2,414	6	56†	8	19	9
Acute leukemia	3,908	0	6	0	78	16
Chronic leukemia	3,891	0	17††	0	45	37

*Data from this report are based on the experience of white patients only. Patients with "carcinoma in situ" and with non-melanotic skin cancers were excluded from the tabulations.

**Some of these patients were also treated with hormones and/or chemotherapy.

***No tumor directed therapy initiated within 4 months of diagnosis. (Such patients may have undergone exploratory surgery or surgery which bypasses the neoplasm without removing tumor tissue. Also, a small number of them may have received tumor directed therapy subsequent to hospital discharge.)

†25% of these patients were also treated with chemotherapy/hormones.

††34% of these patients were also treated with chemotherapy/hormones.

Source: [5]

44. What proportion of new cancer cases receives hospital care?

This question cannot be answered directly because data on hospital care for the entire United States population are not available. However, data collected in the Third National Cancer Survey are helpful in providing some information. All newly diagnosed cancer patients in 1969 through 1971 from a population of over 20,000,000 residents of seven metropolitan areas and two states were surveyed. It was found that the proportion of newly diagnosed cancer patients admitted as inpatients to hospitals had increased to about 96%. In part this reflects the advent of the Medicare and Medicaid programs. Table 23 shows that although the percentage admitted to hospitals in 1969-71 was extremely high, it varied slightly among tumor sites. In general, the chance of hospital admission was below average for patients with highly malignant histologic forms of cancer, extensive regional invasion or metastases, and poor general health or advanced age.

By comparing table 23 with table 22, we see that sites which have a higher proportion of patients not admitted to hospitals also have a higher proportion admitted but not treated. For example,

TABLE 23. PERCENT OF PATIENTS ADMITTED TO HOSPITALS, BY SITE: United States sample, 1969-1971.

SITE	NO. CASES	ADMITTED TO HOSPITAL (%)	NOT ADMITTED TO HOSPITAL (%)*
All sites	193,795	95.5	4.3
Stomach	6,164	93.2	6.8
Colon	18,502	94.8	4.9
Rectum	8,282	95.6	4.2
Pancreas	5,697	92.8	7.2
Lung and Bronchus	23,604	95.0	4.9
Female Breast	25,323	97.1	2.8
Cervix, in-situ	12,022	99.8	0.2
Cervix, Invasive	5,421	97.7	2.2
Corpus uteri	6,920	99.4	0.6
Ovary	4,540	96.5	3.4
Prostate	14,517	95.6	4.4
Bladder	7,733	97.7	2.3
Hodgkin's disease	1,905	98.6	1.4
Acute leukemia	2,367	96.0	3.8
Chronic leukemia	2,270	95.6	4.4

*These patients were either reported by a physician or identified solely through a death certificate.

Source: [11]

TABLE 24. FIVE-YEAR SURVIVAL AND MEDIAN SURVIVAL TIME, BY SITE, 1955-1964.

SITE	ALL STAGES				LOCALIZED			
	NUMBER OF CASES	OBSERVED MEDIAN SURVIVAL TIME (YEARS)	5-YEAR OBSERVED SURVIVAL RATE	5-YEAR RELATIVE SURVIVAL RATE	NUMBER OF CASES	OBSERVED MEDIAN SURVIVAL TIME (YEARS)	5-YEAR OBSERVED SURVIVAL RATE	5-YEAR RELATIVE SURVIVAL RATE
All Sites	219,493	1.7	33	40	88,280	6.7	56	67
Stomach	9,983	0.4	9	12	1,778	1.7	30	39
Colon	19,461	2.2	36	46	7,961	7.1	58	73
Rectum	11,515	2.0	31	40	5,233	5.1	50	64
Pancreas	5,374	0.2	1	1	775	0.3	3	5
Lung and Bronchus	22,585	0.4	7	8	4,193	1.1	24	30
Female Breast	25,698	6.0	54	62	11,478	>10.0	73	84
Cervix uteri	10,557	7.3	55	60	5,451	>10.0	74	79
Corpus uteri	7,614	>10.0	63	72	5,641	>10.0	75	83
Ovary	5,240	1.4	29	32	1,486	>10.0	67	72
Prostate	13,790	3.0	34	51	7,868	4.0	42	64
Bladder	10,177	3.2	42	56	7,645	5.5	52	69
Hodgkin's disease	2,414	2.8	36	39				
Acute leukemia	3,908	0.3	1	1				
Chronic leukemia	3,891	1.6	21	27				

Source: [5]

cancer of the stomach, colon, rectum, pancreas, and lung and bronchus had relatively high percentages of patients not admitted to hospitals and also had high percentages admitted but not receiving definitive treatment: 46, 17, 21, 80 and 29 percent respectively. In comparison, cancer of the breast, bladder, cervix uteri, and corpus uteri had relatively low percentages of patients not admitted and low percentages admitted but not receiving definitive treatment: 4, 8, 6, and 5 percent respectively.

References: [5, 11]

45. What are the chances of survival for cancer patients?

Survival of cancer patients depends on many factors. Two of the most important are the site of the tumor and the degree to which the tumor has spread when treatment started (extent of disease). Others include the age, sex, race, and general health of the patient, and the method of treatment.

Most cancers are diagnosed after middle age. Seventy-six percent of all cancers in men and 63 percent of cancers in women in the United States are diagnosed at age 55 or over. Generally, the outlook for survival decreases with age. However, for cancer patients 15 years of age and under, survival is as low as for patients 65 years of age or older.

The effect of site and stage of disease on survival is seen in table 24. Three measures of survival are presented: observed median survival time, 5-year observed survival rate, and 5-year relative survival rate. The *observed median survival time* is the length of time since diagnosis when half of the patients have died and half are still alive. The *observed survival rate* is the percentage of patients alive at the end of a specific interval of observation after the date of diagnosis. However, the survival rate observed in a group of patients reflects mortality not only from the disease under study, but also deaths due to all other causes. The risk of dying from causes other than the specific cancer under study varies with length of observation, with the sex and age characteristics of the patient group, and with calendar time. The *relative survival rate* adjusts for "normal" mortality, and thus makes possible meaningful comparisons of the survival experience of groups of patients that differ with respect to sex, age, and calendar period of observation. It is defined as the ratio of the observed survival rate to the expected rate for a group of people in the general population similar to the patient group with respect to sex, age, and calendar period of observation. Comparison of relative survival rates provides a measure of differences in mortality associated with specific forms of cancer in patient groups with different "normal" mortality expectations. Examination of each of these measures of survival indicates that survival varies markedly by pri-

mary site of the tumor. Patients with cancer of the corpus uteri, cervix uteri, and breast have the highest observed and relative survival rates and the longest median survival times. On the other hand,

TABLE 25. FIVE-YEAR RELATIVE SURVIVAL RATES, BY STAGE, RACE, SEX, AND SITE, 1955-1964.

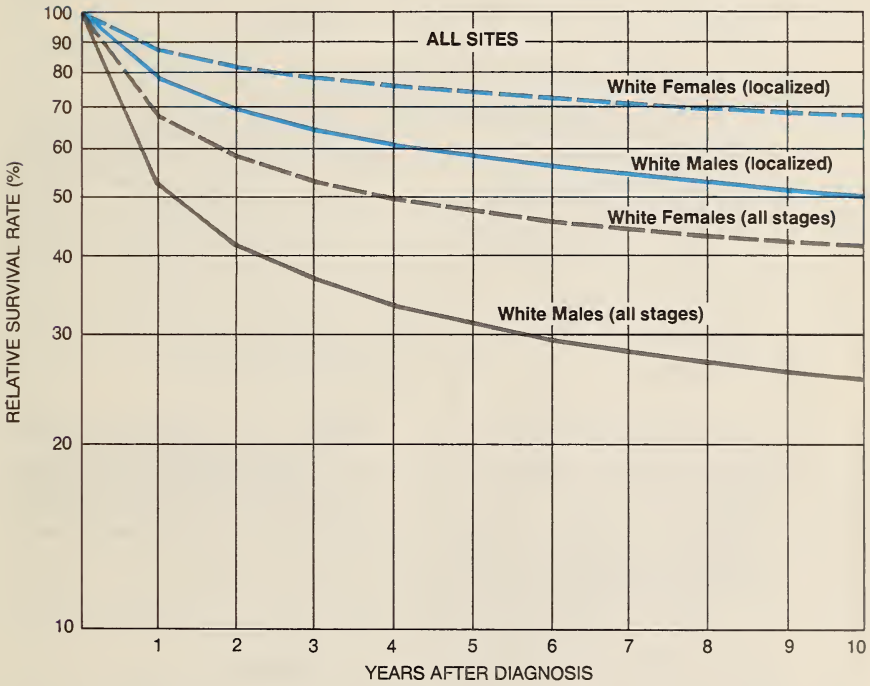
SITE	ALL STAGES				LOCALIZED			
	WHITE		BLACK		WHITE		BLACK	
	MALE	FEMALE	MALE	FEMALE	MALE	FEMALE	MALE	FEMALE
All sites								
No. cases	111,406	108,087	9,861	11,227	42,425	45,855	2,830	3,635
5-year rate	31	47	21	37	59	74	49	69
Stomach								
No. cases	6,337	3,646	918	457	1,077	729	92	50
5-year rate	11	14	8	13	38	41	36*	53*
Colon								
No. cases	8,722	10,739	510	812	3,576	4,403	163	244
5-year rate	43	48	33	38	70	75	61*	69
Rectum								
No. cases	6,298	5,217	350	478	2,897	2,348	126	153
5-year rate	38	41	29	32	62	66	55*	64
Pancreas								
No. cases	3,163	2,211	396	310	443	332	44	43
5-year rate	1	2	1	3	4	5	3*	8*
Lung and Bronchus								
No. cases	19,208	3,377	1,749	364	3,457	642	297	47
5-year rate	8	11	6	6	27	40	23	26*
Female Breast								
No. cases		25,698		2,152		11,564		667
5-year rate		62		47		84		77
Cervix uteri								
No. cases		10,557		2,404		5,490		962
5-year rate		60		51		79		78
Corpus uteri								
No. cases		7,614		660		5,634		337
5-year rate		72		40		83		63
Ovary								
No. cases		5,240		407		1,467		102
5-year rate		32		28		72		74*
Prostate								
No. cases	13,790		1,812		7,860		870	
5-year rate	51		41		64		58	
Bladder								
No. cases	7,499	2,678	382	279	5,699	1,928	202	131
5-year rate	56	56	29	27	68	71	46	48*
Hodgkin's disease								
No. cases	1,394	1,020	112	69				
5-year rate	36	44	23	33*				
Acute leukemia								
No. cases	2,153	1,755	154	132				
5-year rate	1	2	1	3				
Chronic leukemia								
No. cases	2,357	1,534	166	119				
5-year rate	25	29	18	22				

Source: [28] *Rates have a standard error between 5 and 10 percent.

patients with cancer of the pancreas, lung and bronchus, and acute leukemia have the lowest survival rates.

Table 25 shows the 5-year relative survival rates for patients with cancer of sites with the highest incidence, by race, sex, and stage of disease. Relative survival rates are presented so as to ad-

FIGURE 23. RELATIVE SURVIVAL FOR ALL SITES OF CANCER COMBINED, BY STAGE AND SEX: Whites only, diagnosed 1955-1964.



Source: [5]

just for the "normal" mortality expectations of the various sex-race groups of patients. Patients with localized tumors (cancer limited to the site of origin) have more favorable survival rates. The influence of stage is further discussed in Question 46. For most sites, females have higher survival rates than males and whites higher rates than blacks. The marked survival advantage of female patients with cancer is partially attributable to the difference in primary site distribution between males and females. For example, the four leading sites in white males are lung, prostate, colon, and bladder; the 5-year

FIGURE 24. RELATIVE SURVIVAL FOR CANCER OF SELECTED SITES, BY STAGE AND SEX: Whites only, diagnosed 1955-1964.

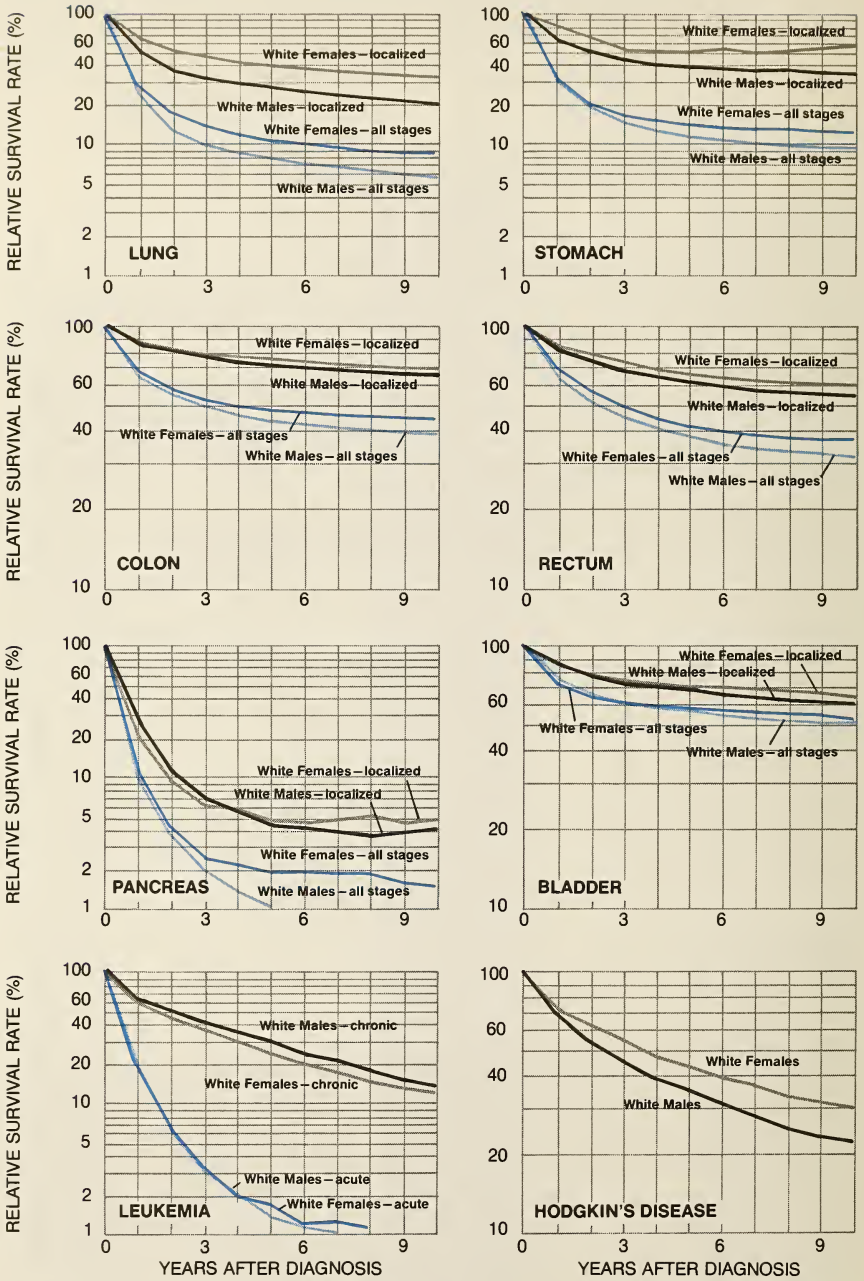


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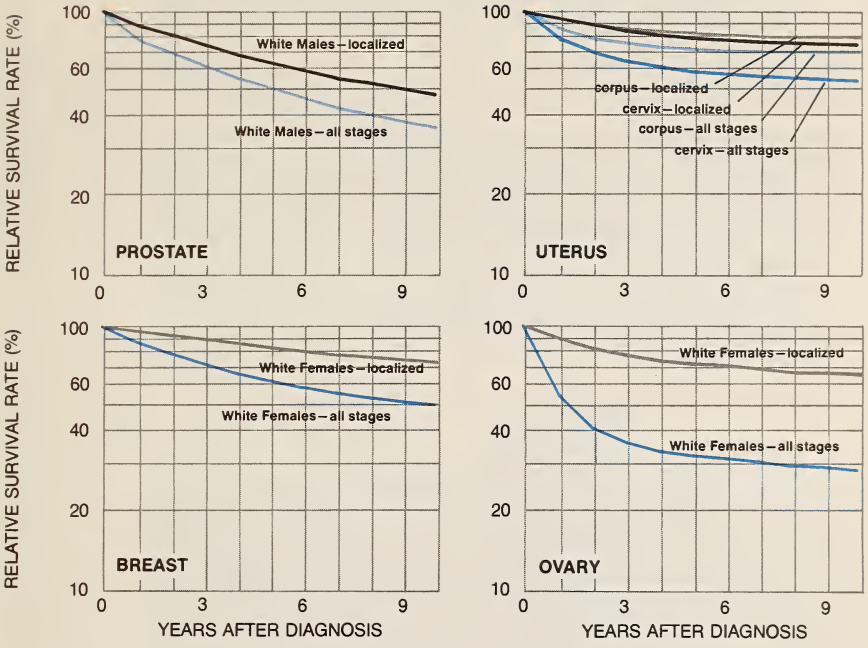
FIGURE 24. *Continued*



relative rates are 8, 51, 43 and 56 percent respectively. The four leading sites in white females are breast, colon, uterine cervix, and uterine corpus; and their survival rates are 62, 48, 60 and 72 percent respectively. Furthermore, when we compare survival of male and female patients for individual sites, we find that females consistently have a more favorable survival.

In order to portray survival patterns for a period of years after diagnosis, survival curves are used. Figures 23 and 24 present relative survival curves for all sites combined and sites with the highest incidence, by stage and sex, plotted on a logarithmic scale. The slope of the relative survival curve reflects changes in the force of cancer mortality. A steep slope indicates that cancer mortality is high; a shallow slope indicates that cancer mortality is moderate. A horizontal curve segment would indicate that excess mortality due to cancer is no longer operative. Examination of the relative survival curves reveals the same relationships as we previously observed, i.e., females have higher survival rates than males and patients with localized tumors have a more favorable survival than patients whose cancers are no longer confined to the site of origin.

References: [5, 28]

46. How does survival depend on the extent to which a cancer has spread?

The prospects of survival are closely related to the extent of tumor spread. In the preceding tables and charts, we compared survival of patients with all stages of disease with that of patients with localized tumors only. We can examine the effect of extent of disease on survival more thoroughly by comparing the survival of patients with localized, regional, and distant disease. Table 26 shows 5-year rela-

TABLE 26. FIVE-YEAR RELATIVE SURVIVAL, BY STAGE OF DISEASE, 1955-1964.

SITE	TOTAL NUMBER OF CASES OBSERVED	5-YEAR RELATIVE SURVIVAL RATE (%)			
		ALL STAGES	LOCALIZED*	REGIONAL**	DISTANT
All sites	219,493	40	67	34	9
Stomach	9,983	12	39	13	2
Colon	19,461	46	73	42	5
Rectum	11,515	40	64	31	4
Pancreas	5,374	1	4	2	0
Lung and Bronchus	22,585	8	30	8	1
Female Breast	25,698	62	84	53	10
Cervix uteri	10,557	60	79	46	12
Corpus uteri	7,614	72	83	50	14
Ovary	5,240	32	72	36	8
Prostate	13,790	51	64	51	17
Bladder	10,177	56	69	21	4

*Localized cancer is defined as cancer limited to the site of origin.
**Regional involvement is defined as cancer which has spread to regional lymph nodes, adjacent organs or tissues, or both.

Source: Unpublished data from [5]

tive survival rates for cancer patients diagnosed during 1955-64 for selected sites by stage. The stage classification is based on all information available during the first course of treatment. Patients with localized tumors have the best survival rates, and the rates decrease in direct relation to extent of disease. It is important to note that accuracy of the assessment of extent of disease is influenced by the frequency with which diagnostic and treatment methods such as exploration and surgical resection are used. For example, information on extent of spread for cancer of the cervix may be more

TABLE 27. TIME TRENDS IN PERCENTAGE OF CANCER PATIENTS WITH LOCALIZED DISEASE AT DIAGNOSIS AND PERCENTAGE TREATED SURGICALLY.

SITE	1940-49			1950-54			1955-64			1965-69		
	NUMBER OF CASES	% LOC.	% SURG.	NUMBER OF CASES	% LOC.	% SURG.	NUMBER OF CASES	% LOC.	% SURG.	NUMBER OF CASES	% LOC.	% SURG.
Stomach	6,567	20	31	5,166	15	42	9,983	18	46	3,889	18	48
Colon	7,066	36	58	7,525	38	76	19,461	41	81	10,152	42	84
Rectum	6,154	37	55	5,604	42	72	11,515	45	76	5,512	46	78
Pancreas	1,989	19	20	2,046	13	21	5,374	14	8	2,888	11	10
Lung & Bronchus	4,264	18	11	6,663	17	20	22,585	19	26	15,941	18	27
Female Breast	12,696	38	81	11,886	41	84	25,698	45	88	14,911	47	90
Cervix uteri	6,988	44	12	5,963	52	23	10,557	52	22	4,888	47	22
Corpus uteri	3,632	62	55	3,486	69	69	7,614	74	75	4,400	78	79
Ovary	2,476	26	61	2,259	26	63	5,240	28	68	3,085	27	71
Prostate	4,845	46	60	5,212	51	59	13,790	57	61	7,384	63	64
Bladder	3,898	66	70	3,975	67	81	10,177	75	85	5,295	79	87
Melanoma of skin	754	54	73	924	56	83	2,862	68	91	1,996	73	93

Source: [5-8]

accurate for surgically treated patients than for those treated by radiotherapy.

References: [5]

47. Has the proportion of patients with localized tumor involvement increased in recent years?

Early detection, while the cancer is localized or limited to the organ of origin, offers the best opportunity for control. Consequently, in recent years, much emphasis has been placed on early detection. One would expect the emphasis on early detection to be reflected by an increase in the proportion of cancer patients diagnosed with localized disease in the later years. However, it is difficult to compare the percentage of patients with localized tumors for different time periods because diagnostic and treatment practices and completeness of case reporting have changed. For example, table 27 shows that the percentage of patients receiving surgical resection within four months after diagnosis has generally increased over time. The increased use of surgical resection is partly responsible for the more accurate stage classification in recent years.

Since stage classification has been more accurate in the later years, time trends in the percentage of patients with localized tumors at diagnosis must be examined cautiously. There are only a few sites for which there has been a noteworthy reported increase in the percent of cancers diagnosed as localized: breast, prostate, bladder, corpus uteri, and melanoma of the skin (table 27). The increase in the percent of melanoma patients diagnosed as localized may be partly due to the increased frequency of histologic examination of suspicious looking nevi removed in recent years. Although there has been no substantial increase in the proportion of patients diagnosed with localized tumors of the cervix uteri, there has been a significant increase in the proportion of patients with tumors of the cervix detected in the in-situ stage. The widespread use of the Pap smear in screening for cancer of the cervix uteri has contributed greatly to this increase. For cancer of the lung and bronchus and colon, there has been little change since the 1940's in the proportion of cases classified as localized at diagnosis. However, the percentage of lung and colon cancers treated surgically increased substantially, resulting in more accurate staging. The percentage of localized pancreatic cancer cases decreased markedly between the 1940's and 1950's, probably because of more frequent detection of metastatic spread during the 1950's and thereafter than in earlier years.

References: [5-8]

48. Has the survival of cancer patients improved in recent years?

There has been significant improvement in survival rates for cancer of several sites. In table 28, 3-year relative survival rates are presented by date of diagnosis. Three-year rates were chosen to illustrate time trends in survival. At the time the data were compiled, reliable rates beyond 3 years were not available for patients diagnosed during the most recent period, 1965-69. The data indicate a sustained, significant increase in the survival rates for patients whose cancers were diagnosed in 1965-69 over the rates of those diagnosed in 1940-49 and 1950-59 for cancers of the following sites: larynx, prostate, bladder, melanoma of skin, thyroid, Hodgkin's disease, multiple myeloma, acute leukemia, and chronic leukemia. The greatest improvement in survival occurred between the 1940's and 1950's. The observed improvement is largely attributable to advances in treatment and to supportive techniques which made increased use of surgery possible. Also, the increase in the percentage of patients diagnosed with localized tumors between the 1940's and 1950's was partly responsible for the improved survival in the 1950's. Survival continued to improve from the 1950's to the late 1960's, but to a lesser degree.

The upward trend in the 1-year survival rate for children under 15 years of age with leukemia indicates continuing progress and provides hope for further improvement. The 1-year rate increased from 36 percent in 1955-64 to 59 percent in 1965-69. Among children with acute lymphocytic leukemia diagnosed in 1965-69, the survival rate was 67 percent. Due to greatly improved methods of chemotherapy, radiation technique, and life support systems, the 3-year survival rate for children with acute lymphocytic leukemia has increased from less than 6 percent to 15 percent over the past 10 years.

The outlook has also improved for patients with cancers of the breast, colon, and rectum. For all stages of breast cancer, the 3-year survival rate has increased from 63 percent 20 years ago to 72 percent in the most recent time period. However, since the 1950's, survival has not shown continued improvement. Three-year survival rates for patients with cancers of the colon and rectum have increased from 1940-49 to 1950-59, but have also leveled off in the past decade.

There has been some improvement in survival for patients with lung cancer, but no improvement for patients with cancer of the pancreas. Lung cancer is the most common male cancer with 64,000 new cases and 57,900 deaths annually among United States men, and incidence is still increasing. The 3-year survival rate in the 1940's was 6 percent as compared to 11 percent in 1965-69. Treat-

TABLE 28. TIME TREND IN THREE-YEAR RELATIVE SURVIVAL, BY SITE.

SITE	1940-49		1950-59		1965-69	
	NO. CASES	3-YEAR SURVIVAL (%)	NO. CASES	3-YEAR SURVIVAL (%)	NO. CASES	3-YEAR SURVIVAL (%)
Stomach	7,390	12	9,987	15	3,889	15
Colon	7,488	36	16,153	49	10,152	50
Rectum	6,979	35	10,901	47	5,512	49
Pancreas	2,009	2	4,391	2	2,888	2
Larynx	1,462	47	3,259	60	2,725	67
Lung and Bronchus	4,772	6	16,072	10	15,941	11
Female Breast	12,184	63	22,105	71	14,911	72
Cervix uteri	7,075	53	10,280	64	4,888	63
Corpus uteri	3,509	66	6,529	74	4,400	76
Ovary	2,339	30	4,296	33	3,085	35
Prostate	6,008	49	11,647	59	7,384	66
Bladder	4,337	48	8,350	58	5,295	62
Melanoma of Skin	749	49	1,982	63	1,996	74
Brain & cranial meninges	2,437	28	4,679	28	3,810	37
Thyroid	697	67	2,377	81	1,445	86
Hodgkin's disease	1,013	35	2,008	44	1,990	61
Multiple myeloma	391	10	1,328	13	1,116	27
Acute leukemia	922	4	2,837	14	2,432	30
Chronic leukemia	1,599	24	3,627	35	1,587	41

Source: [5]

ment results for localized forms of the disease have shown greater improvement. The 3-year rate has increased from 17 percent in the 1940's to 39 percent in 1965-69.

Survival rates for cancer of the pancreas have shown no improvement over the past 20 years. The 3-year survival rate of the 1940's, 2 percent, for all stages of this disease has not risen in recent times. Even when detected in the early stages, the 3-year survival rate has remained at about 4 percent.

Survival curves for patients diagnosed in successive calendar periods from 1940 to 1969 are shown in figure 25 for the more frequently occurring forms of cancer.

References: [5-8]

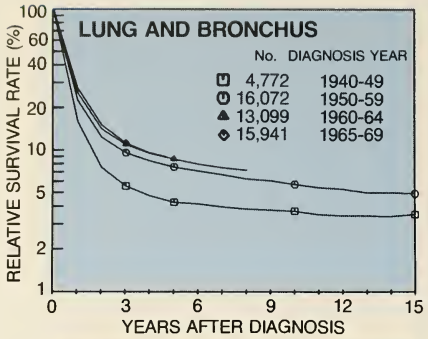
49. How much would the elimination of cancer as a cause of death benefit society and the population?

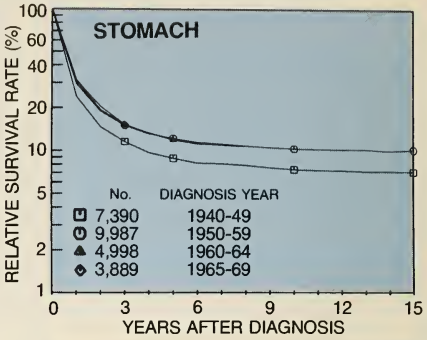
There are several ways to measure the impact that the elimination of cancer deaths would have on society and the population. First, if mortality from cancer were eliminated, the average length of life of the general population would be increased by more than two years. This is calculated by comparing the current life expectancy of the general population subject to mortality from all causes to that of the general population with deaths from cancer eliminated. However, the size of such an increase would depend on the patient's sex and age, as shown in figure 26. The increase would also depend to some degree on many other factors related to cancer mortality, such as race, marital status and place of residence. The calculated increase in life expectancy is based on current mortality rates from cancer and from other causes. If these mortality rates change significantly, the effect of cancer on average longevity could be altered. On the average, the life expectancy of persons with cancer is reduced approximately 16 years as a direct result of their disease; this average reduction is less for elderly cancer patients and greater for young patients.

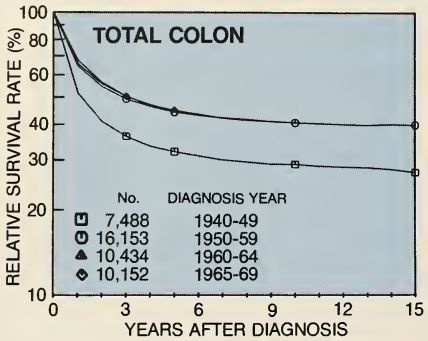
Another approach used to measure the impact of eradicating cancer mortality is to examine the gain in work-years if death from cancer were eliminated. Assuming that a person's working life is between ages 20 and 65, approximately 1.8 million work-years would be gained each year in the United States if deaths from cancer were eliminated. The number of work-years gained would vary with each type of cancer. In addition, the total economic cost of cancer (including direct expenditure, indirect cost of morbidity and the value of lifetime earnings), which is estimated at over 18.9 billion dollars, would be saved each year.

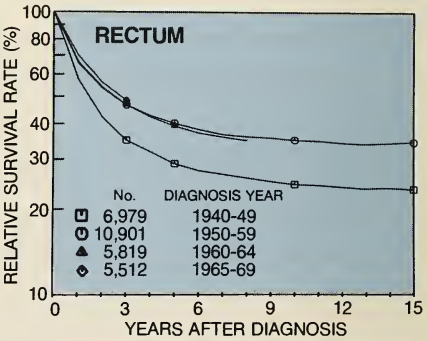
References: [13, 137]

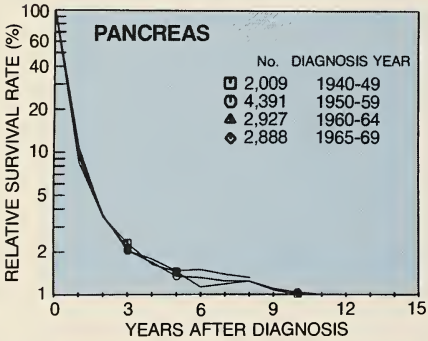
FIGURE 25. RELATIVE SURVIVAL FOR CANCER OF SELECTED SITES, BY YEAR OF DIAGNOSIS.

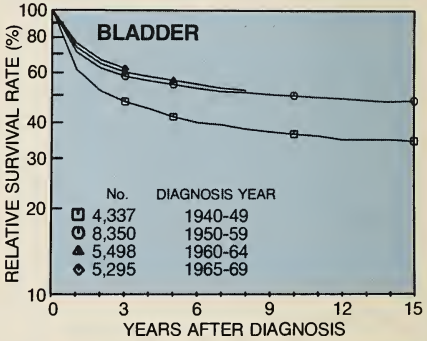


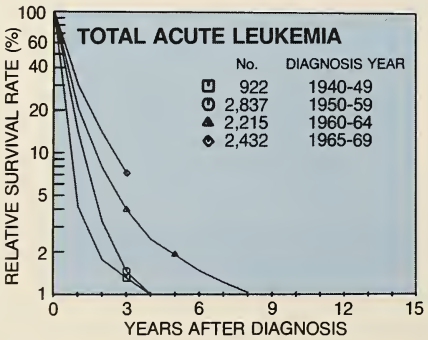












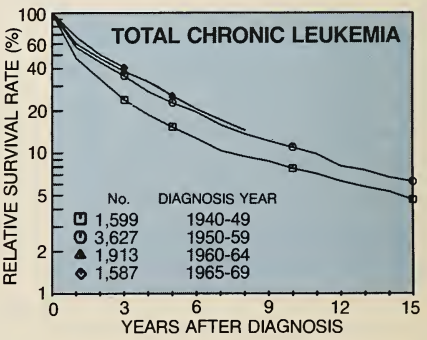
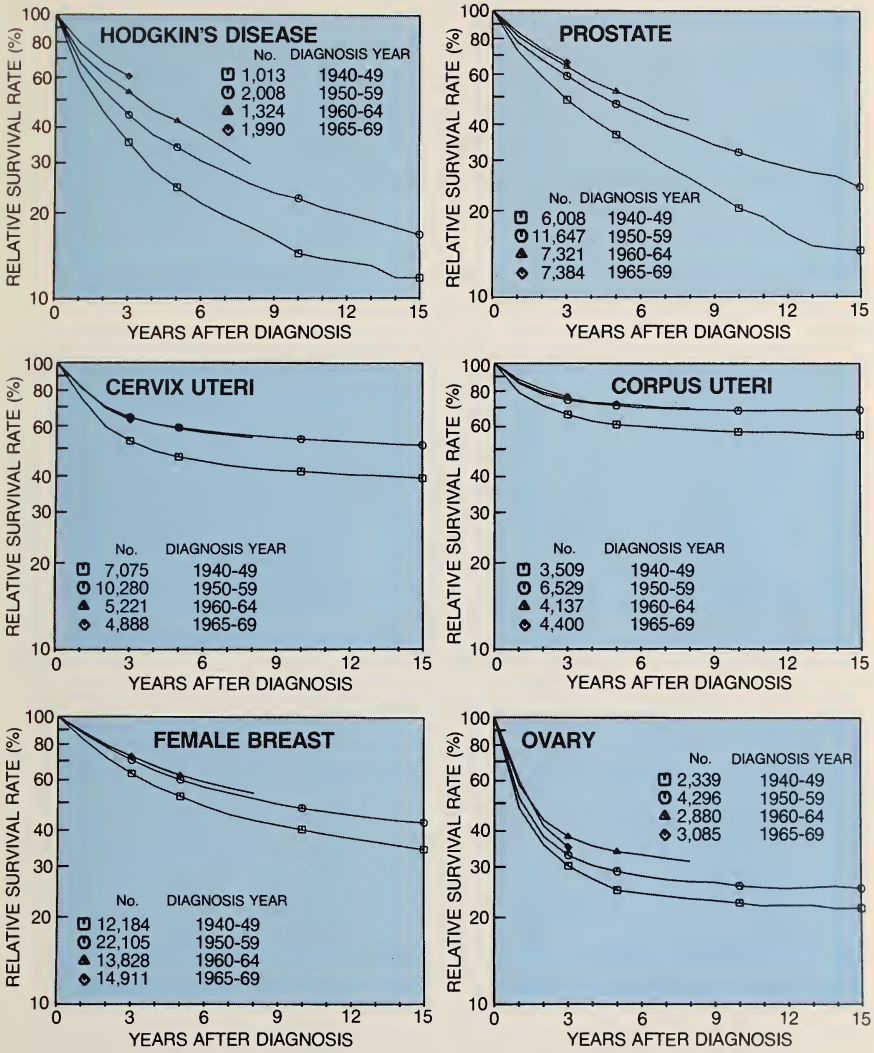


FIGURE 25. *Continued*



Source: [5-8]

50. What are the prospects for reducing the toll from cancer?

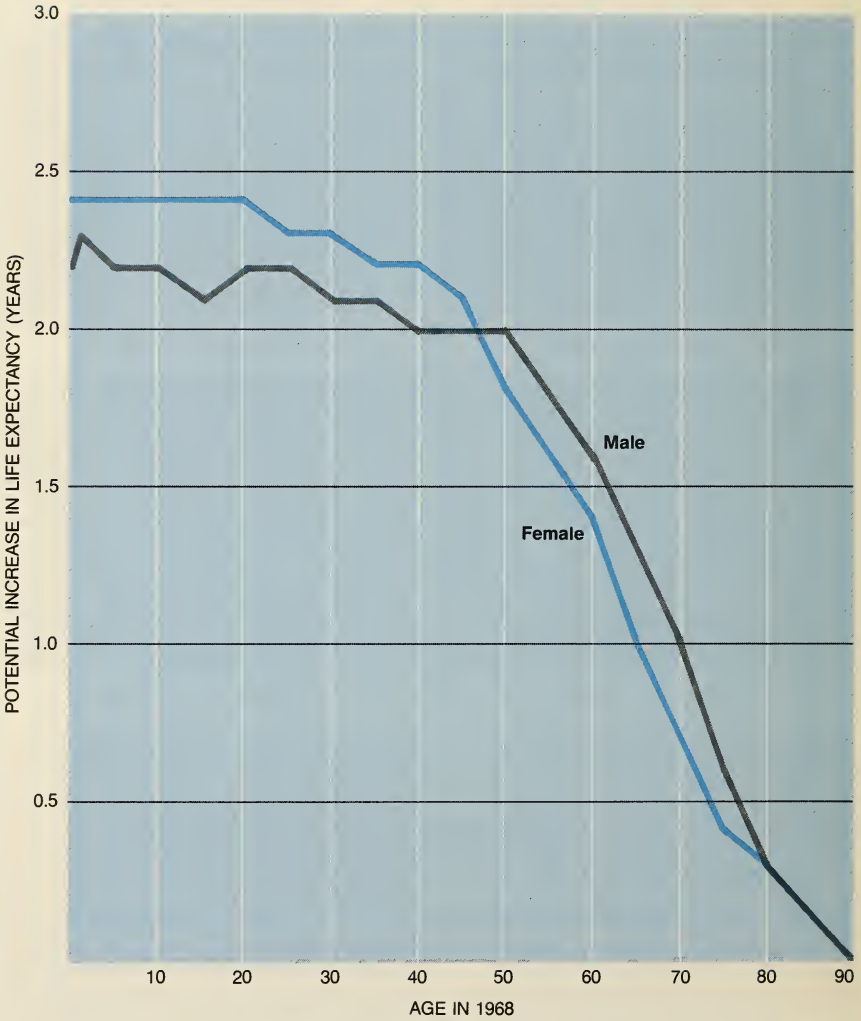
There are only three avenues by which the toll of cancer illness and death can be controlled and reduced: prevention, earlier detection, and improvements in treatment.

Existing knowledge, if implemented, makes cancer prevention on a large scale a feasible goal for two important cancer sites, lung

and cervix. If all persons would stop smoking cigarettes and if all women would have cytologic examination of the cervix at regular intervals, there is every reason to expect a large and immediate reduction in cervical cancer mortality and a somewhat slower but no less impressive reduction in lung cancer mortality. Avoidance of all unnecessary exposure to drugs and other possible environmental carcinogens would lower incidence of other cancers.

Earlier detection is already feasible for nearly all forms of can-

FIGURE 26. INCREASE IN LIFE EXPECTANCY IF CANCER DEATHS WERE ELIMINATED, BY SEX AND AGE: United States, 1968.



Source: calculated from unpublished data from [11]

cer. Greater alertness on the part of practicing physicians, more widespread availability and use of radiographic and other diagnostic techniques, and—most important—education of the public to seek medical advice at an earlier stage would, when combined with vigorous investigation of all suspected lesions, result in significant increases in the survival of patients with most forms of cancer.

During the past few decades there have been striking advances in cancer therapy, and there is good reason to hope that this progress will continue. However, many patients with metastatic cancer are beyond cure by any conceivable extension of present surgical and radiological techniques. The best hope for such patients now lies in the development of completely new methods of treating cancer, perhaps by chemotherapeutic or immunologic methods. Research in these areas is expected to lead to better treatment of cancer patients.

In assessing the possibilities for reducing the toll from cancer, one should always bear in mind that cancer is not a single disease. Each type of cancer has its own distinctive causes and characteristics. Any quick and universal solution to all these various forms of cancer seems extremely unlikely, despite widespread hopes and expectations to the contrary. However, the value of current step-by-step progress must not be underestimated. Forty years ago a cancer patient had a 20 percent chance of surviving 5 years; today the figure is 33 percent, and prospects are very good for continued improvement in the decades to come. These values are based on observed 5-year survival including all causes of death. When adjustment is made for the fact that cancer patients die of other causes, a "relative survival" figure is obtained: a cancer patient today has a 40 percent chance of avoiding death due to his cancer for a period of 5 years following diagnosis.

Medical research provides no easy guarantee and no predetermined timetable of success; but with skill, resourcefulness, and perseverance, it provides the basis for current progress and the best hope of eventual success. We may hope that the steady accumulation of medical knowledge will eventually reduce the threat of cancer to the same proportions as other once feared diseases such as tuberculosis, smallpox, and the plague.

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